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ENTEROVIRUSES IN SEWAGE AND EPIDEMIC POLIOMYELITIS IN EASTERN CANADA*

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THE DETECTION of enteroviruses in sewage promises to be a tool of epidemiologic value in tracing the gross spread of enteroviral agents throughout a community. This aspect acquires added importance when it is related to the consequences of possible future large-scale oral polio vaccination programs now being contemplated in various parts of the world. If oral polio vaccine is to be used in future, as an adjunct to intensive programs of Salk vaccination, in the face of a threatened epidemic, then the periodic examination of sewage for enterovirus will become an important function of regional virus laboratories. Thus, the appearance of wild poliovirus in sewage may herald the start of an epidemic of paralytic poliomyelitis.

Poliovirus was originally demonstrated in sewage by Paul, Trask and Culotta[1] in 1939. Since this date, comparatively few data have been published on the techniques of isolation and the significance of enteroviral surveillance of communal sewage. In 1940 Gard[2] showed that virus could be recovered from sewage after precipitation by ammonium sulphate and dialysis of the precipitate The method of virus isolation rested on the demonstration of typical histopathological lesions in the spinal cord of monkeys. The early report of Rhodes *et al.* in 1950[3] showed that the isolation of poliovirus from city sewage was followed by a severe paralytic epidemic.

Melnick *et al.*, in 1954,[4] described elaborate procedures for demonstrating the presence of Coxsackie viruses in sewage, using suckling mice. Kelly, Winsser and Winkelstein, Jr., in 1957,[5] recovered enteroviruses from gauze swabs suspended in flowing sewage for two to seven days. The fluid was expressed from the swabs, adsorbed and then eluted from ion exchange resins. Antibiotics were added to the eluate which was then frozen and stored. Ether was added to thawed eluates, centrifuged, and then tested in suckling mice and tissue culture. Of 308 sewage samples tested, Poliovirus types 1, 2 and 3 were found in 21% of the samples, Coxsackie viruses in 42%, mixtures of polio and Coxsackie viruses in 13%, and unidentified agents in 3%. Kelly *et al.*[5] suggested that there was no obvious correlation between the presence of poliovirus in sewage, reported paralytic cases, and the socio-economic status of the community.

Bloom *et al.* (1959)[6] examined a total of 1018 sewage samples over a two-year period and identified a range of viruses present including Poliovirus types 1 and 3 and ECHO virus types 1, 3, 4, 6, 7, 8, 9 and 14, as well as numerous untyped Coxsackie viruses. Their study centred round the examination of sewage in various stages of treatment at a sewage disposal plant and it was of interest that virus isolates were present in all stages of sewage treatment, including the final effluent. In this respect it should be noted that Clarke and Kabler (1954)[7] reported that purified Coxsackie virus was 7 to 46 times less susceptible to free chlorine than a suspension of *E. coli*. Clarke and Kaber felt that virus in sewage could be protected by extraneous organic matter and hence that the effectiveness of chlorine treatment of effluent depended upon its ability to penetrate organic matter.

METHODS AND MATERIALS

The routine isolation of agents from patients with enteroviral disease was carried out using standard procedures as reported previously.[8] Cell lines included monolayer monkey cell cultures, HeLa, and human amnion cells. Suckling mice passages were performed as required. Sera used in typing neutralization tests were obtained from Microbiological Associates and from the Laboratory of Hygiene, Department of National Health and Welfare, Ottawa.

Specimens of sewage were collected from cities and towns in the local area during the months of June to September 1960. Weekly specimens were obtained over a period of four to six weeks, and repeat specimens were collected at the same site. Single samples were also received. The sewage was collected by submerging sterile screw-cap 4-6

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oz. water sampling bottles in flowing sewage. With the exception of sewage submitted from the city of St. John's, Newfoundland, which was chlorinated, all sewage processed was untreated. Specimens received from long distances were immediately frozen and shipped in dry ice. Several specimens were sent unfrozen after collection, involving a total travel time of 12 to 24 hours. If the specimens were not processed immediately upon receipt by the laboratory, they were stored at –25° C.

The sedimented material was resuspended by manual stirring to yield a more representative sample. Aliquots were centrifuged at 4000 to 5000 r.p.m. for one hour in a refrigerated centrifuge. The supernate was then removed and divided into two portions, one of which was used directly in isolation procedures. The other portion was transferred to standard lusteroid cellulose (Spinco) ultracentrifuge tubes and centrifuged for 2½ hours at 39,000 r.p.m. The supernate from these tubes was discarded and the deposit resuspended in 1 ml. of phosphate buffered saline or a maintenance medium closely resembling that described by Morgan, Morton and Parker (1950).[9] The resuspended sediment represented an approximate x13 concentration of the original sewage. *For isolation procedures,* two types of samples were used. The first consisted of supernate after centrifugation at 4000 to 5000 r.p.m. for one hour. The second was derived after further centrifugation of the supernate at 39,000 r.p.m. for 2½ hours and resuspension of the deposit. The purpose of this procedure was to compare the sensitivity of the two methods. Then 0.5 ml. of the resuspended sewage centrifugate was inoculated to washed monolayer tube cultures of monkey kidney epithelium cells in standard 16 x 125 mm. screw-cap tubes. The cultures were allowed to stand for one hour at room temperature and then 1.0 ml. of monkey kidney maintenance medium (modified Morgan's medium[9] plus tryptose broth supplement) was added. The tubes were then incubated at 37° C. and examined daily for cytopathic effect. A culture showing no evidence of viral cytopathology at the end of six to eight days received a blind passage, bringing the total culture period to a minimum of 14 days.

When a cytopathic effect (CPE) was evident in the culture tubes, the specimens were divided into two groups. The first was typed directly in monolayer tube cultures, using standard tube neutralization procedures. *For typing tests,* antisera against Coxsackie A9, Coxsackie B1, 2, 3, 4 and 5, Echo virus types 1-19, and Poliovirus types 1, 2 and 3 were used. In those instances where the enteroviral CPE was not neutralized by any of these sera, the typing procedure was repeated, using limiting dilutions of the viral isolate.

The second group of cultures, representing the bulk of this report, were inoculated to monkey kidney epithelium plaque culture bottles in the following manner. For virus plaque isolation, monkey kidney monolayer cultures were grown in a 4-oz. medicine bottle with white rubber stopper. The bottles were seeded with 3.5 x 10^5 cells per ml. in 10 ml. of growth fluid consisting of modified Morgan's medium;[9] 5% tryptose broth, 5% calf serum, plus the following antibiotics: penicillin 500 u./ml. and streptomycin 500 μg./ml. After seven to nine days of growth the tissue cultures were ready for passage of virus material. The cell sheet was washed twice with Hanks lactalbumin hydrolysate (0.5% lactal. hyd.). The viral material for passage was diluted in concentrations of 10^{-3} to 10^{-9} in maintenance medium or phosphate buffered saline, and inoculated to the bare tissue culture sheet, using two bottles per dilution. The inoculum consisting of 0.3 ml. per bottle was allowed to stand at room temperature for one hour, and during this interval the bottles were tilted and rotated at 15-minute intervals. At the end of this time, the dye-agar overlay at a temperature of 41° C. was added. The agar medium resembled that described by Hsiung and Melnick[10] but with a final dye concentration of 1:20,000. Monkey serum and calf serum were added to the medium in concentrations of 4% and 2% respectively. With this serum concentration good cell viability was maintained for periods of two weeks, with dyed agar at the stated concentration. The culture bottles were incubated at 37° C. until optimal plaque formation became evident, usually between three and 14 days.

When plaques developed, they were picked off with curved Pasteur pipettes, and inoculated to monkey kidney monolayer tube cultures. The isolate from the tube culture was the virus used in typing. After harvesting of the initial crop of plaques, usually evident within four to seven days after incubation, the bottles were reincubated up to 16 days to await the formation of possible late virus plaques in the same culture.

After identification of the virus present in highest titre (or with the greatest selective adsorption), the material was repassaged in plaque cultures blocked with the appropriate antiserum. This was done by taking 0.5 ml. aliquots of the virus dilutions at 10^{-3} to 10^{-9} and adding equal amounts of appropriate antiserum. The blocking serum-virus mixture, after standing for one hour, was then used as inoculum (0.3 ml.) on the plaque culture bottles as described above. This method helped to eliminate the problem of differentiating virus mixtures in material of high titre virus content.

Frequently, many plaques developed in one bottle. To save time and to avoid the laborious procedure of typing each individual plaque, a tube neutralization typing procedure was carried out on the most representative plaque in the culture. The original isolate was then reinoculated at varying dilution into plaque culture bottles after first blocking with the appropriate antiserum. In this way from 75 to 80% of plaque formation could be eliminated without the need for individual typing procedures on each. The effect of late plaquing virus could then become evident in these cultures.

TABLE I.—VIRUS ISOLATIONS FROM SEWAGE, ATLANTIC PROVINCES, CANADA, 1960 - 61

Town	*Population*	*Tube culture*	*Plaque culture*	*Month*
Amherst, N.S.	10,300	Poliovirus 1		July 5/60
		Unidentified virus		July 26/60
		Coxsackie A9	Poliovirus 3 + Unidentified	Aug. 24/60
			ECHO 7	Sept. 7/60
			ECHO 7 + Coxsackie B2	Sept. 29/60
		Unidentified virus		Oct. 4/60
Charlottetown, P.E.I.	16,700	ECHO 7		Aug. 13/60
		Coxsackie B3		Aug. 13/60
Summerside, P.E.I.	7,420	Coxsackie B4		Aug. 13/60
		Coxsackie B3		Aug. 13/60
		Unidentified virus		Aug. 13/60
Dartmouth, N.S.	48,000	Poliovirus 1		July 29/60
		Poliovirus 1		Aug. 10/60
		Coxsackie A9		Aug. 16/60
		Poliovirus 3		Aug. 26/60
Sydney, N.S.	32,200	ECHO 2		July 14/60
			ECHO 17	July 19/60
		Coxsackie B4		Aug. 25/60
		Unidentified virus		Aug. 25/60
		Coxsackie B4		Aug. 25/60
			ECHO 7	Sept. 1/60
St. John's, Nfld.	85,000		ECHO 7	Sept. 23/60
			ECHO 7	Sept. 23/60
			ECHO 7	Sept. 23/60
			Coxsackie B2	Sept. 23/60
		ECHO 14		Sept. 23/60
Cornerbrook, Nfld.	23,220		Poliovirus 1	Sept. 23/60
			Poliovirus 1	Sept. 23/60

The possible elution effect of inocula at higher dilutions did not appear to be a major problem in these studies.

RESULTS

Effects of high vs. low speed centrifugation. The results obtained using sewage that had been centrifuged at 4000-5000 r.p.m. were compared with the resuspended deposit of such material after it had been centrifuged at 39,000 r.p.m for 2½ hours. From a total of 56 sewage specimens passed on tissue culture, in 17 instances a viral isolation was successful by both methods. In 11 cultures, only the ultracentrifuged specimens showed evidence of viral CPE; in one instance, only the non-ultracentrifuged material showed viral CPE. In 27 specimens no cytopathic effect was obtained by either method. Thus, from a total of 56 sewage cultures, CPE was obtained in 29, of which 28 were noted in ultracentrifuged specimens and 18 after standard centrifugation.

It is evident that, in untreated sewage at least, a fairly high rate of viral isolation can be obtained without the necessity of ultracentrifugation, but the results obtained by the latter technique are superior.

Virus isolation from sewage. The specimens taken in 1960-61 included untreated sewage effluent from a number of towns as well as specimens from septic tanks of several consolidated schools. The sewage specimens were received during the months of July through September 1960, beginning on July 5 and continuing to October 4, 1960. The specimens from septic tanks of consolidated schools were obtained during the winter months from December 29, 1960, to March 6, 1961. These latter specimens were obtained from the western end of the province of Nova Scotia as part of an enteroviral surveillance program designed to determine prevalent virus in the area, prior to an experimental trial of oral poliomyelitis vaccine. These results will be reported later. The results of virus isolations are summarized in Table I. The range of virus isolations from these sources has included Poliovirus types 1 and 3; Coxsackie virus types B2, B3, B4 and A9; ECHO virus types 2, 7, 14 and 17.

Several points of interest may be noted in the tabulated results. The town of Amherst, with a population of 10,300, lies adjacent to the border of the neighbouring province of New Brunswick. The latter province experienced a moderate but widely scattered epidemic of paralytic poliomyelitis due to Poliovirus type 3. This epidemic began early in the summer of 1960. In a village close to the town of Amherst, beginning early in June 1960, there was a small outbreak of type 1 paralytic disease. This did not result in an instance of paralytic disease in the town of Amherst. Poliovirus type 1 was detected in later specimens taken through to October 4. Amherst did not experience any paralytic disease of Poliovirus type 3 etiology, but the virus was detected in the sewage on August 24, 1960, in a single specimen associated with Coxsackie virus type A9 and an unidentified enterovirus. In this specimen the poliovirus was detected by plaque culture after blocking out the Coxsackie A9 virus. In a specimen taken one week later, and

others continuing through the month of October, poliovirus was no longer detectable and the September isolates consisted of ECHO virus type 7 and Coxsackie virus type B2.

From the city of Dartmouth, N.S., population 48,000, Poliovirus type 1 was detected in repeated specimens during the months of July and August, one month after a small type 1 paralytic epidemic had occurred 100 miles to the west. A mixture of Coxsackie virus type A9 and Poliovirus type 3 was detected in the city sewage during the latter half of August. From the town of Dartmouth, there was only one recorded case of paralytic type 3 poliomyelitis during the latter half of August, and during this same period only one recorded case of paralysis due to Poliovirus type 1.

Sewage as untreated effluent from the city of Sydney, N.S., population 32,200, was examined during the months of July to September inclusive. There were no recorded cases of paralytic poliomyelitis in the area, and poliovirus was not detected. There were repeated isolations of Coxsackie virus type B4 in the month of August, and ECHO virus type 7 was isolated in the month of September.

In Newfoundland, specimens were received from two sources, St. John's (pop. 58,000) in the extreme eastern end of the province and Cornerbrook (pop. 23,225) in the western end of the province, situated over 400 road miles apart. During the summer of 1959, the St. John's area experienced a severe epidemic of paralytic poliomyelitis with a high attack rate.[11] During the same summer the town of Cornerbrook, on the other hand, and the western end of Newfoundland generally, did not experience this epidemic, but suffered a small epidemic of pleurodynia and aseptic meningitis associated with infection by Coxsackie virus type B5. In the succeeding summer, 1960, there were no recorded paralytic poliomyelitis cases in St. John's, but Cornerbrook experienced a fairly severe epidemic of paralytic disease due to Poliovirus type 1. As might be expected, sewage from Cornerbrook in the month of September 1960 readily yielded Poliovirus type 1 and no other viral agent was detected. During the same month effluent from St. John's yielded ECHO virus type 7, Coxsackie virus type B2, and ECHO virus type 14; no poliovirus was detected from this area.

Repeated sewage specimens from Newfoundland which were cultured during the month of April 1960 failed to yield virus by routine isolation methods. On the other hand, specimens taken during the winter months, January 1960 to March 1961, from septic tanks of consolidated schools in the western end of Nova Scotia yielded ECHO virus type 7.

Virus isolations from human case material.—Table II shows the enteroviral isolations from human infections in the four Atlantic Provinces during the years 1958-1960. These include both cases of clinical disease and asymptomatic contacts. The range of virus isolates includes Poliovirus types 1 and 3, each type of which has been responsible for a paralytic epidemic during these years; Coxsackie virus types B2, B3, B4, B5, A7, A9 and A16 and ECHO virus types, 2, 6, 7, 9, 11, 13, 14, 15, 19 and 25. During this same period of time the most frequently encountered isolations have been Poliovirus types 1 and 3, Coxsackie virus types B2, B3, B4, B5 and A9, and ECHO virus types 6, 7 and 14. It may be seen that with but two exceptions (Coxsackie B5 and ECHO type 6) all the viruses in the latter group have been detected in the sewage specimens during the summer of 1960. The only additional virus detected in sewage which was not isolated from individuals was ECHO virus type 17.

TABLE II.—ENTEROVIRAL ISOLATIONS FROM HUMAN INFECTIONS IN ATLANTIC PROVINCES, CANADA, 1958 - 60

Province	*Year*	*Poliovirus*	*Coxsackie virus*	*ECHO virus*
Nova Scotia	1958		B5 (1)	
	1959	Type 1 (13) Type 3 (7)	B5 (14) A16 (1)	Type 7 (1) Type 14 (12) Type 6 (3) Type 19 (2)
	1960	Type 1 (39) Type 3 (2)	B5 (2) B2 (6) A9 (4)	Type 13 (1) Type 6 (2)
Prince Edward Is.	1959	Type 1 (1)		
	1960		A9 (1)	
New Brunswick	1958		A7 (1)	Type 14 (1)
	1959	Type 1 (1) Type 3 (1)		
	1960	Type 1 (2) Type 3 (16)*	B5 (1)	Type 15 (1) Type 6 (2)
Newfoundland	1958			Type 9 (3) Type 25 (2) Type 2 (1)
	1959	Type 1 (142)* Type 3 (1)	B3 (7) B4 (5) B5 (7) A9 (5)	Type 14 (8) Type 11 (3) Type 7 (2)
	1960	Type 1 (33)*	B4 (1)	Type 6 (2) Type 7 (7) Type 13 (1)

*Epidemic in progress.

Virus mixtures.—Plaque cultures were undertaken in an effort to determine whether they could resolve virus mixtures more readily than the standard techniques of terminal dilution purification and blocking with appropriate antisera. By either technique, very few mixtures were encountered or elicited in the present study, that is, within a single sewage specimen. On the other hand, different viral content was easily demonstrable in specimens taken from different sources in any particular town on the same day.

Two sets of virus mixtures were identified in single specimens during the course of this study. One mixture contained Coxsackie virus type A9, Poliovirus type 3 and an unidentified enterovirus. The identity of the former virus was determined through terminal dilution purification; the latter two viruses were obtained from adjacent plaques in the same dilution, 10^{-6}, of an A9-blocked inoculum. This was the only example we obtained of the plaque isolation of a virus mixture at the same

dilution. Another combination encountered was that of ECHO virus type 7 and Coxsackie virus type B2. In this case the serial dilution for plaque culture helped to separate them. The ECHO virus was isolated at a dilution of 10^{-4} and the Coxsackie virus at a dilution of 10^{-6}. In general it could be stated that with two exceptions all plaque harvests from a single specimen consisted of only one virus type. The theoretical probability of encountering mixed viruses in different titre, showing varying selective adsorption to living cell cultures, occurring as plaques in a single specimen, is remote. There are several theoretical reasons for the difficulties encountered in the resolution of mixed viral inocula in tissue culture. In standard tube tests the problem of selective adsorption results in overgrowth by one type (not necessarily the virus of the highest titre) over another. On the other hand, if by chance, viral replication of two agents with similar rates of attachment to cells results in a mixed culture, then standard typing procedures fail to separate them. Sommerville[12] has shown the variation between rates of attachment of several ECHO virus types on monkey kidney cells, indicating for example that ECHO virus type 7 has a faster rate of attachment than ECHO virus types 1, 2 and 11. Further studies of this type comparing various ECHO viruses, Coxsackie viruses and polioviruses under controlled conditions are necessary. In plaque cultures, plaque formers in mixed culture are difficult to recognize, and the inoculation of suspect viral mixtures at varying dilution may help to overcome this. In one example, from a single specimen an early plaquing ECHO 7 virus was isolated at a lower dilution, while a later plaquing Coxsackie B2 virus was shown in the same culture at a higher dilution.

DISCUSSION

An effort has been made to correlate human epidemiological data with enteroviruses isolated from sewage. During the past two years, the Atlantic Provinces have had varying experience with respect to enteroviral epidemiology. New Brunswick and Newfoundland have suffered fairly severe paralytic poliomyelitis epidemics of two different virus types. The other two provinces, during the same period of time, escaped epidemic paralytic illness. During the inter-epidemic years, the enteroviral experience in all four provinces has been remarkably similar, indicating the ubiquitous distribution of these viruses. There seems to be no consistent pattern of distribution of the non-polio enteroviral agents in relation to paralytic poliomyelitis epidemics.

It is noteworthy that Poliovirus type 2 has been absent from the Atlantic Provinces for several years and we have failed to demonstrate it in sewage. In the towns where poliovirus was prevalent in the summer of 1960, as found in sewage, no Coxsackie B virus isolations were made simultaneously, but appeared later after poliovirus ceased to be recovered.

ECHO virus type 7 was detectable later in the fall from widely scattered points and was also present in mid-winter from cultures of consolidated school septic tanks. According to Kelly *et al.*,[5] enterovirus in sewage bears little relationship to local enteroviral epidemiology. Perhaps the lack of such correlation may well be attributed to technical problems concerned in examination of sewage for virus. In our own example, the range of enteroviral causes of human illness during the past four years has been much more extensive than the range of agents we were able to demonstrate in sewage during one summer. On the other hand, if we considered only those agents which were most often encountered in the form of human disease during the past two years, with but two exceptions the same range of enterovirus was recovered in sewage. If enough specimens of sewage are examined, it is conceivable that many more agents will be found than can be accounted for by recognized virus-diagnosed human infections either in sporadic or epidemic form, since the ratio of subclinical to clinical enterovirus infection may be very high.[13]

Current evidence indicates that the oral attenuated poliovirus strains now under test promise to arrest the spread of wild virus throughout a population.[14] Their effectiveness as antigens in inducing a lasting immunity to paralytic poliomyelitis may take many years to prove. From studies, using the Cox-Lederle vaccine strains[15] and the Sabin strains,[16, 17] it is evident that oral vaccination is only partially successful in abolishing the capacity to be reinfected, at least by attenuated strains of poliovirus. It is conceivable, therefore, that despite the use of combined Salk and oral immunization schedules in the future, a reservoir of wild virulent poliovirus may continue to be maintained in our populations. This will necessitate vaccination on a mass scale with oral vaccines as the percentage of susceptibles in the population increases. The cyclic susceptibility of population areas to paralytic poliomyelitis varies considerably and is probably dependent upon a number of factors including climate, population density, age distribution, and sanitary and other conditions facilitating spread of virus. One important factor, however, which may be overlooked is the prevalent pattern of infection with other enteroviruses in "silent" asymptomatic form. In North America, Poliovirus type 2 may serve during certain summer periods to keep the population free of paralytic type 1 epidemics. Such "silent" viral infection may vary from one geographical area to another and so introduce an unpredictable factor which may make it difficult to estimate the periods at which a significant proportion of the population will acquire susceptibility to paralytic poliomyelitis. The use of attenuated viral agents to supplant the natural virulent poliovirus may result in shorter cycles of population

susceptibility. As such it may be that annual examinations of sewage for virus at weekly intervals at the beginning of the poliomyelitis season may offer a guide in deciding when to revaccinate an area in the face of an impending paralytic poliomyelitis epidemic. If, on the other hand, the oral vaccines are given as boosters to infants, following Salk vaccination, and the vaccine virus survives in sewage, then it will be important to differentiate between vaccine and wild poliovirus strains. This will have to be accomplished either by neutralization kinetic studies or by the use of genetic markers.

Preliminary reports on studies by Wehrle, Hagen and Carbonaro[18] indicate that the transmission of attenuated vaccine poliovirus is very limited. The latter authors were unable to detect the virus in sewage collected from a school where children were orally vaccinated with type 3 poliovirus vaccine.

CONCLUSIONS

The routine examination of communal sewage for wild polioviruses promises to offer a procedure whereby some estimate of the susceptibility of a community to poliovirus infection may be gauged. If and when mass oral vaccination programs are to be adopted, as an adjunct to Salk vaccination, the presence or absence of wild polioviruses in sewage may guide public health authorities in deciding when and where to institute an oral vaccination program.

Examination of sewage in conjunction with the search for enteroviruses in the stools of sick patients may prove to be a valuable laboratory tool for the medical officer of health in determining communal enteroviral epidemiology.

In the present data, correlation exists between the most prevalent and widespread causes of enteroviral human illness in an area and enterovirus isolations from sewage.

During the years 1959-1960 a range of Coxsackie and ECHO viruses were recovered from sewage and from sick patients in the Atlantic Provinces. From the pattern of their distribution in Nova Scotia, there was no evidence to suggest that these viruses offered cross-protection against paralytic poliomyelitis.

The technique of plaque cultivation does not offer an advantage over standard limiting dilution purification techniques in resolving mixed viral inocula encountered in the examination of sewage for enterovirus.

Despite the absence of a paralytic poliomyelitis epidemic in Nova Scotia in the summer of 1960, both type 1 and type 3 Polioviruses were demonstrated in sewage specimens. The isolation of the type 3 Poliovirus coincided in time with the paralytic type 3 epidemic which occurred in New Brunswick during the same summer.

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PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

THE TORONTO ACADEMY OF MEDICINE

The formal opening of the new premises of the Toronto Academy of Medicine took place October 27th. The presidential address was given by Dr. N. A. Powell. The academy was formed five years ago by the amalgamation of four separate bodies: the Toronto Medical Society, the Clinical Society, the Pathological Society, and the Ontario Medical Library Association. The academy's new premises cover a lot 264 feet by 107, with room for its meetings, its library, and its growth generally. Dr. Osler described the site as the finest location for a central home of the profession in any city in America . . .

On Tuesday, October 31st, the academy was addressed by Dr. C. N. B. Camac, of New York, on the subject of "The Out-patient Clinic". Dr. Camac traced the history of his subject in a most interesting way. The first dispensary was established in 1687, and in 1696 a public subscription list included many great names. Under the original system, physicians prescribed for the poor without charge . . .

Since earliest days, medical and economic objections have been urged against the dispensary system. The argument was used that it was a money making scheme: that the public were pauperized; that they were cheated by indiscriminate drugging. Some of these objections have still some foundation and attempts have been made to minimize evils which are occasionally apparent. A New York law to prevent, under penalty, people of means attending free clinics has proved unavailing.—*Canad. M. A. J.*, 1: 1217 and 1224, 1911.

EXPERIMENTAL IMMUNOLOGIC LIVER INJURY AND THE CONCEPT OF AUTODESTRUCTION*

PART II

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THE FIRST part of this paper[70] dealt with experimentally induced lesions of the liver caused by the interaction of non-specific antigens and their respective antibodies in the hepatic circulation. This process was designated as non-specific, since neither of the immunologically active substances possessed any known affinity for liver tissue.

This second part will be concerned with the so-called specific forms of allergic liver injury caused by either circulating or "cell-bound" antibodies which have a known affinity for liver tissue or which are assumed to possess one. To lay a proper basis for these considerations, the question of the antigenicity of liver tissue will be examined from an immunologic standpoint. Further, since Freund's adjuvant (a water-in-oil suspension of *Mycobacterial* residues) has been the substance of choice in attempts to enhance the antigenicity of isologous liver homogenates, its effect on the liver will be examined as a corollary to studies of the so-called isoimmune injury.

EXPERIMENTAL IMMUNOLOGIC LIVER INJURY

A. *Antigenicity of Liver Tissue—Immunologic Aspects*

Until the introduction of ultracentrifugation, the characterization or liver antigens was difficult to achieve, owing to the extreme complexity of the antigenic structure of the liver as an organ. Most tests of antigenicity were carried out by means of *heterologous systems* (antigens of one species injected into animals of another species).

It was shown that antibodies produced in rabbits against rat liver tissue could be neutralized by rat kidney and vice versa.[7] Attempts to produce a liver-specific antibody failed.[20] When rat liver tissue homogenates were allowed to undergo autolytic changes *in vitro* (37° C.) for 24 hours and were then administered to rabbits, the resulting antibodies cross-reacted with rat liver homogenates, with rat serum proteins as well as with rat kidney, lung and heart extracts.[20] It was further shown that a severe toxic liver injury did not necessarily lead to an alteration of the antigenic structure of the liver. Antibodies developing in rabbits against liver tissue of rats, previously damaged by the action of carbon tetrachloride, cross-reacted with autolysates of various organs of both normal and carbon-tetrachloride-treated rats.[21] Frank and Bozsoky[21] concluded that heterologous antibodies against normal and CCl_4-altered tissues were identical. Attempts at purification of liver antigens failed in the initial stages. Phospholipid extracts of rat liver gave rise to heterologous antibodies which lacked specificity for liver tissue.[41, 65] D'Amelio and Perlmann[14] subsequently showed that the microsomal fraction of liver cells, obtained by ultracentrifugation, contained 10-15 immunologically distinct proteins. These antigens were found to be physicochemically and immunologically distinct from rat serum proteins. When the quantitative precipitin test was employed, using the microsomal fraction of rat liver cells and a corresponding rabbit antibody, evidence was produced that this fraction contains unequivocal liver-specific antigens.[81] Mitochondria, nuclei and the soluble cytoplasmic fraction of rat liver cells do not contain measurable amounts of such tissue-specific antigens.[82] Finally, evidence was produced that the specific-tissue antigen resides in the membranes (and not in the RNP particles) of the endoplasmic reticulum.[83]

It is pertinent to stress that these immunologic investigations are far ahead of any morphologic attempts to produce an injury by a specific anti-liver serum. All such investigations, with the exception of one,[89] employ crude liver homogenates. These will be analyzed anon.

Using a *homologous system*, Vorlaender[84] was able to show that an autolysate of rabbit liver tissue injected into rabbits together with an adjuvant of tubercle bacilli, gave rise to isoantibodies in the recipients. The antibodies were liver-specific if the autolysate was injected less than 48 hours after removal from the organism. The specificity was lost after 96 hours' incubation when such anti-liver antibodies were shown to cross-react with kidney homogenates.[85] These observations were confirmed by others.[25]

As early as 1907, liver *autoantibodies* were demonstrated in a rabbit suffering from distomiasis.[9] Similar autoantibodies were also said to appear in the serum of rabbits receiving carbon tetrachloride.[11] However, recent investigations[29] have cast doubt upon the specificity of these antibodies, since rats injected with rat liver suspensions in Freund's adjuvant developed anti-kidney antibodies and incidentally a nephrotic renal disease.

The value of these immunologic investigations was to lay the theoretical foundation upon which are based studies of the pathogenicity of heterologous, homologous and isologous antibodies.

B. *Injury by Heterologous Anti-cellular Antibodies*

The experiments included under this heading utilize the principle that tissues or cells of a donor

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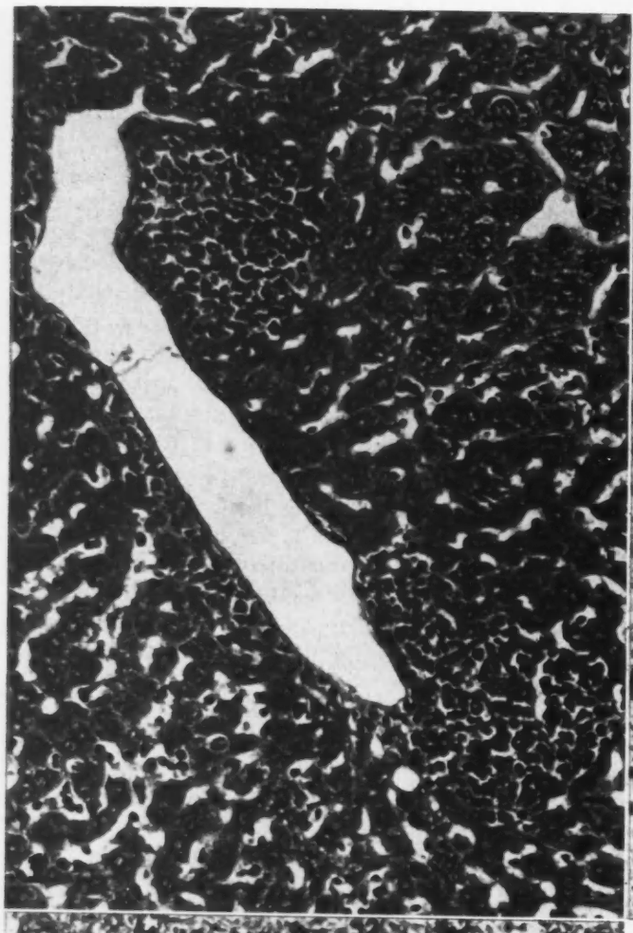

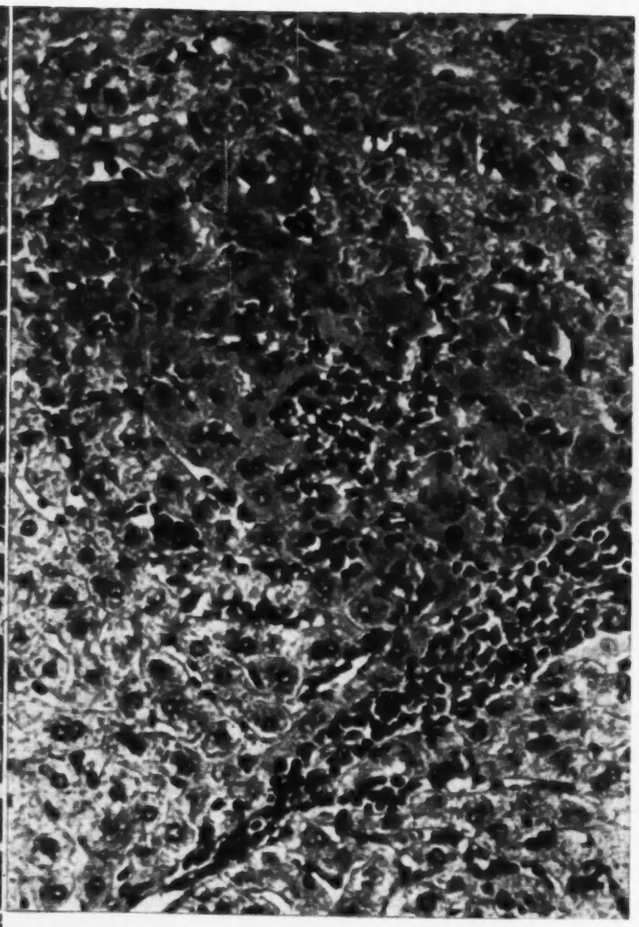

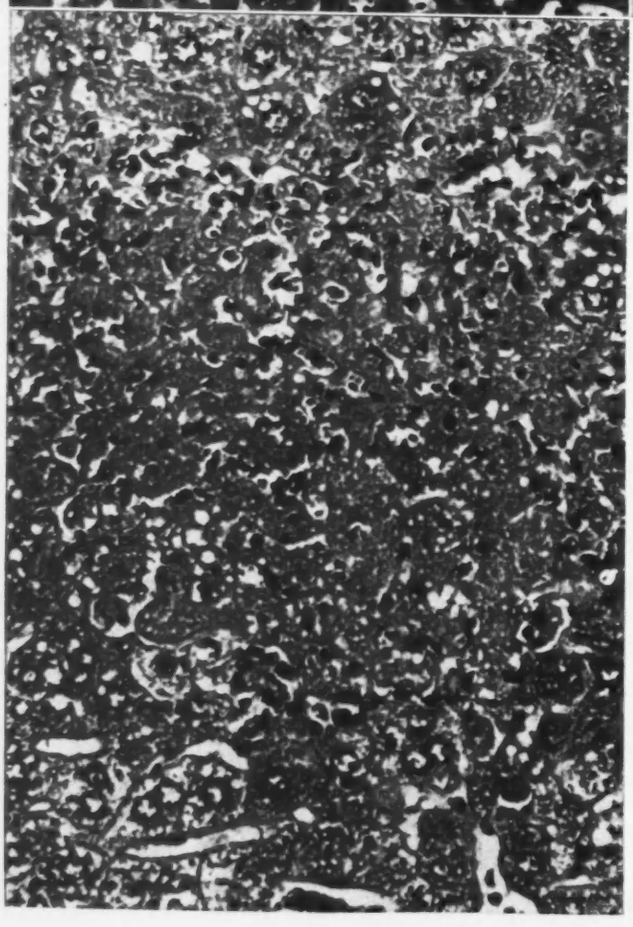

Fig. 1.—Mouse. Single intravenous injection of heterologous, rabbit anti-mouse liver, serum—24 hours. Aggregation of mesenchymal cells around portal veins. (Compare with Fig. 9 in Part I of this paper.) Hematoxylin and eosin, × 221.

Fig. 2.—Same procedure as Fig. 1—24 hours. Focal area of eosinophilic degeneration of parenchymal cells with moderate mesenchymal cell reaction. Hematoxylin and eosin, × 305.

Fig. 3.—Same procedure as Fig. 2—48 hours. Coagulative necrosis of focal area in midzone of a lobule. This change is seen only rarely. Hematoxylin and eosin, × 305.

animal of one species injected into a recipient of another species will lead to the development of anti-tissue antibodies in the latter's serum. Such antisera will produce injury upon re-injection into another animal of the original donor species.

The events following upon injection of a heterologous anti-tissue serum are complex. They are compounded by two factors:

1. The presence of undesirable antibodies, e.g. anti-erythrocyte, anti-serum, Forssman antibodies, etc.

2. The heterologous antiserum is itself an antigen and may lead to the development of a non-specific immunologic injury of a type described above.

We will consider the injury produced by anti-erythrocyte and anti-liver antibodies, respectively, and then examine the evidence of specificity of such antibodies from a morphologic point of view.

I. *The Effect of Heterologous Anti-erythrocyte Antibodies*

Rabbits immunized with canine erythrocytes, bile or blood-containing organs yielded antisera which upon re-injection into dogs produced mid-zonal or peripheral liver necroses. The necrosis was described as "hyalin" in character without fragmentation of cords of liver cells. Conglutinative thrombi present within the lumina of sinusoids were interpreted as resulting from the activity of hemolytic and hemo-agglutinative antibodies.[52-54] Karsner and Aub[33] produced similar antibodies by injecting rabbits with defibrinated blood of cats. Administration of the rabbit antiserum to normal cats led to development of hyalin necroses which were said to differ from the "granular" necroses produced by the injection of inert particulate materials, e.g. lycopodium, carmine or animal charcoal, into the portal veins of animals.[42]

It was concluded[33] that obstruction of sinusoids by agglutinated erythrocytes was not the only cause of the necroses. Since they could not be produced by the injection of erythrocytes agglutinated *in vitro*, it was suggested that during agglutination occurring *in vivo*, corpuscles lodged in sinusoids released sufficient amboceptor (cytolysin) to produce a serious effect on liver cells.

Others, however, considered the necroses, caused by repeated injections of heterologous erythrocytes (hamster red blood cells into rabbits[6]) or of hemolytic sera into heterologous animals,[30, 56, 80] as being the direct result of thrombosis of sinusoids by agglutinated red cells.

II. *The Effect of Heterologous Anti-liver Sera*

Delezenne[16] was the first to use a hepatotoxic serum produced by the administration of dog liver to rabbits and subsequent re-injection of the rabbit anti-dog-liver serum into dogs. Deutsch carried out similar experiments with a rabbit-guinea-pig combination of animals.[17] Delezenne[16] considered activity of this serum to be organ-specific, since no lesions were found in organs other than the liver. These consisted of fatty degeneration, necrosis and round cell infiltration. Although the animals developed no icterus or hemoglobinemia, their urine contained tyrosine and leucine and occasionally glucose. Others[36] repeated this experiment and found no hepatic lesions despite the presence of icterus and hemoglobinemia. Fukuhura[27] found no evidence of retention of bile in the liver but demonstrated occasional small areas of necrosis.

These experiments were repeated using a cat-rabbit combination of animals. The rabbit anti-cat-liver serum produced fatty metamorphosis and replacement fibrosis of entire lobules in the cat. This occurred one to four months after the initial injection.[32] Masugi,[43-45] in his now famous experiments, used nephrotoxic as well as hepatoxic sera. His technique was an improvement on previous methods, since after producing an anti-rat-liver serum in rabbits, he removed from this antiserum antibodies active against rat erythrocytes and serum components. The residual antiserum had no precipitin titre for erythrocytes, a titre of 80 for rat serum and 320 for rat liver. After injections of massive doses of this serum to rats, lesions were found within 24-48 hours in the periphery of lobules. They consisted of hyaline degenerations and hemorrhagic necroses. Hyaline thrombi were found in sinusoids. When smaller doses were used there was endothelial proliferation and a leukocytic and lymphocytic infiltration. Masugi considered the lesions to be ischemic in origin caused by thrombosis of sinusoids. Estes[18] repeated these experiments, injecting small doses (0.3 ml.) of a rabbit anti-rat-liver serum into rats every other day for three months and larger doses (2 ml.) for up to two weeks. The only animals which developed lesions were those receiving 2 ml. on one or two occasions (sacrificed 48 hours after the last injection). Only focal areas of necrosis were noted with a slight cellular infiltration. Since lesions could not be found in animals sacrificed later, Estes suggested that only the first dose was pathogenic and that subsequently the animals became tolerant to hepatotoxins.

Yokouti[89] refined these procedures by producing two types of duck anti-rabbit liver sera. One produced against the cytoplasm of liver cells reacted electively with the cytoplasm of rabbit liver cells. An anti-liver cell-nuclear serum reacted with both nuclei and cytoplasm of parenchymal cells. Both sera produced necroses and mesenchymal cell reactions after being administered to rabbits in a single massive dose. Others, using dogs and rats as donors, and rabbits as recipients, considered hydropic degeneration of parenchymal cells as the principal evidence of heterologous injury.[47]

Our own experiments[71] have shown that when moderate doses of anti-liver sera are used, degenerative and necrotic lesions (Figs. 2 and 3) are produced only rarely in rabbit-dog, guinea-pig—rat and rabbit-mouse combinations of animals. The sera were absorbed with donor red cells and inactivated at 50° C. for half an hour. Proliferations of mesenchymal cells were seen in all recipient animals (Fig. 1) and were most marked in mice, but they were in no way different from those resulting from the injection of foreign sera with no specific affinity for liver tissue. However, this mesenchymal reaction tended to appear as rapidly as after injections of soluble complexes formed in antigen excess.

III. *The Specificity of Anti-liver Sera*

The specificity of anti-liver antibodies has been doubted by many on pathologic and theoretical grounds:

1. When dog-rabbit, mouse-rabbit or cat-rabbit combinations of animals are used, Forssman antibodies may distort the histologic picture.[85] In fact, when Forssman antibodies were removed from

sera, lesions could not be produced despite the use of potent anti-liver sera. Letterer, quoted by Vorlaender,[85] dismissed the heterologous liver injury as neither theoretically nor practically significant. He suggested that the liver, unlike the kidney, possessed a great resistance to immunologic injury.

2. Meyer-Krahmer[2, 47] repeated Masugi's experiments. He considered that the injury was due to a direct cytotoxic activity of the antiserum rather than to ischemia. However, he established that the injury is not specific, since a myotoxic serum (rabbit anti-dog skeletal muscle serum) induced identical liver changes. The histology of the lesion was not affected by the removal of anti-erythrocyte and anti-serum antibodies. He went so far as to suggest that any anti-tissue antiserum would probably damage the liver because of its special anatomic and physiologic position and role in the organism.

3. Yokouti[89] reviewed the Japanese literature on the subject and pointed out the divergence of views on the specificity of heterologous antisera. Whereas some investigators claimed to have produced a liver injury only, others reported that hepatotoxic sera would produce a liver as well as a kidney injury. The only specific anti-liver serum was one which was formed in response to injections of parenchymal liver cell cytoplasm to heterologous animals. An admixture of mesenchymal elements led to the development of sera which could be neutralized by other than liver tissue, thus rendering them non-pathogenic.

4. When isotopic labelling was used in the investigation of heterologous sera, their cross-reactivity became more clearly apparent. Heterologous anti-liver sera are partly bound to tissues other than the liver and, conversely, anti-aorta and anti-kidney antibodies become partly localized in the liver.[35, 61] These cross-reacting antibodies can be reduced in an anti-liver serum by absorption with a preparation of liver blood vessels. The resulting purified antiserum shows a greater affinity for liver cells than the original antibody.[60]

IV. *Comparison with Human Lesions*

The lesions produced in the liver by heterologous antisera have been likened to those occurring in: (i) icterus gravis neonatorum,[34, 90] (ii) eclampsia,[44] (iii) phosphorus poisoning,[16] (iv) acute yellow atrophy.[16]

This variety of pathologic lesions attests to the variable results of injections of heterologous anti-liver sera in experimental animals.

V. *Conclusions*

1. Crude liver homogenates injected into heterologous animals stimulate the production of a variety of antibodies. Re-injection of such antisera into the original donor species produces liver injury.

2. Cellular infiltrations in the liver of animals receiving a heterologous antiserum cannot be interpreted as specific evidence of activity of such a serum, since they are probably merely a response to the injections of a foreign serum (i.e. a non-specific immunologic injury). They develop, however, at an accelerated rate.

3. Cellular degenerations and necroses are non-specific phenomena, since they can be produced not only by anti-liver antibodies but also by myotoxic and anti-erythrocyte sera. Their development probably depends to some extent on the quantity of antiserum employed. Only the first injection of a heterologous antiserum is probably damaging. Animals develop a resistance or tolerance to subsequent injections.

4. The lesions may be due to vascular occlusion by thrombi initiated by anti-erythrocyte or anti-serum antibodies or they may be due to a direct cytotoxic effect.

5. Heterologous anti-liver antibodies are not organ-specific. The liver shares common antigens with other tissues, e.g. blood vessels and kidney.

6. Owing to the extreme complexity of the factors determining the development of this type of injury and the inconsistent results obtained by various investigations, this experimental model contributes little to the understanding of the pathogenesis of allergic liver injury. It is unlikely to be of significant value as a prototype of human liver injury.

C. *Freund's Adjuvant*

The introduction by Freund and McDermott[22] of emulsified adjuvants containing acid-fast bacilli has provided a vehicle whereby isoimmunization and autoimmunization to various tissues can be readily induced in experimental animals. The mechanisms of enhancement of antibody production and the imparting of antigenicity by an adjuvant to tissue components normally non-antigenic[24] is not clear. It has been suggested that this capacity is dependent upon the dispersal of an antigen through the organism in a form (water-in-oil emulsion) which resists removal and ensures retention of antigens in tissue.[23] Others considered the mononuclear reaction provoked by the adjuvant to be of importance.[26] The possible tuberculin-like sensitization imparted by the mycobacterial fraction to an antigen or hapten was stressed.[63] We have suggested the possibility that the intense proliferation of immunologically competent cells induced by an injection of the adjuvant may increase the chances of adverse mutations of such cells. Consequently, mutant "forbidden" clones may emerge which fail to recognize normally non-antigenic materials and react to them immunologically.[72] This concept was in accord with Burnet's Theory of Acquired Immunity.[8]

We have shown[72] that, when Freund's adjuvant is administered to rabbits intracutaneously, intramuscularly or intravenously, disseminated granulomata developed in the liver (Figs. 4 and 5) as well as in other organs. Multiple sections of the liver had to be examined before such miliary

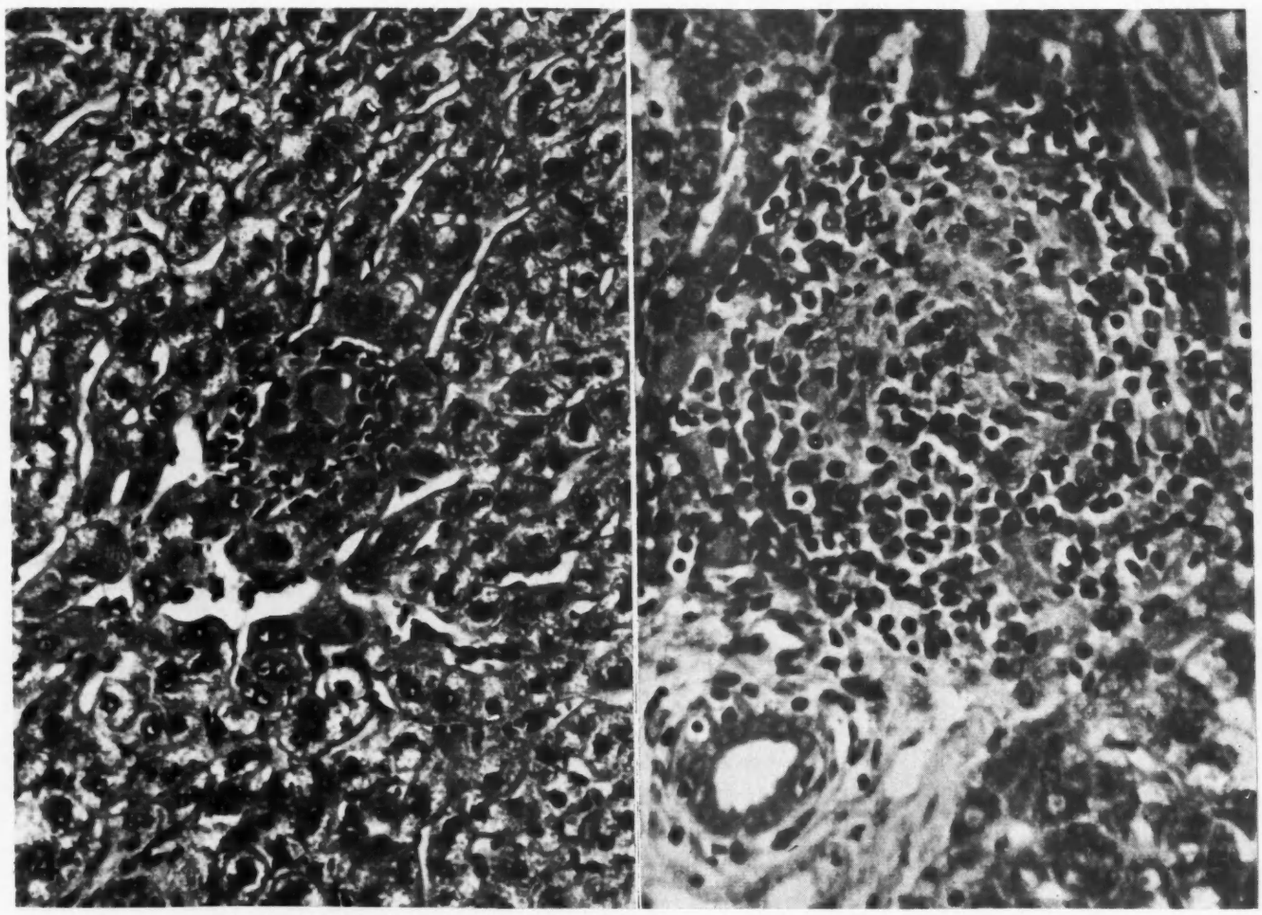

Fig. 4.—Rabbit. Single intramuscular injection of Freund's adjuvant. Focal non-caseating tuberculoid granuloma in midzone of lobule. A Langhans-type giant cell occupies centre of the lesion. Hematoxylin and eosin, × 305. **Fig. 5.**—Same procedure as Fig. 4. Focal peripheral granuloma adjacent to portal tract. Although active necrosis of parenchymal cells cannot be seen it is probable that such a process accompanied the formation of the lesion. Azure eosin, × 420.

nodules were found. These consisted of non-caseating tubercles resembling the lesions of sarcoidosis[10] in midzonal and peripheral lobular locations. In addition more diffuse cellular infiltrates in lobules and in the connective tissue of portal tracts were continuous with cuffs of mononuclear cells around bile ducts and ductules.[72] Others injected rabbits with Freund's adjuvant intravenously and demonstrated a proliferation and accumulation of reticuloendothelial (RE) cells in liver sinusoids.[64] In mice, subcutaneous injections of the adjuvant lead also to proliferation of mononuclear and histiocytic cells in portal spaces and these infiltrate lobules.[37] Similar lesions were also found in guinea-pigs and hamsters.[1, 37] Only mice developed occasionally hepatic amyloidosis.[37] Pearson[55] demonstrated epithelioid granulomas in the livers of 20% of rats injected with Freund's adjuvant into the footpad. He also noted occasional necrotic or organizing foci.

With the exception of the last-mentioned report, necrosis of the liver was not reported. It was admitted, however, that degenerative changes of liver cells (hydropic, acidophilic and fatty degeneration) may be due to the adjuvant in guinea-pigs and hamsters.[1] One report recorded the occurrence of hyalin necroses in three of ten guinea-pigs injected with the adjuvant alone.[49]

Freund's adjuvant has been used to potentiate the dormant antigenicity of liver tissue in all investigations of the so-called isoimmune liver injury. The morphologic alterations due to the adjuvant alone must be subtracted from any alterations thought to be produced by the potentiated liver antigen.

D. *Experimental "Isoimmune" Liver Injury*

Experiments included under this heading utilize the principle that liver tissue of an individual of a species or of an inbred strain of animals, potentiated by an adjuvant, injected into another member of the species or strain, will lead to immunization and to development of lesions.

Symeonidis[77] tested the effects of isoimmunization in mice. When fragments of liver tissue were transplanted into normal animals and into other previously sensitized with mouse liver breis, the cellular reaction around the transplant and its necrosis developed more rapidly in the latter than in the former. Starzl *et al.*[69] have shown that a liver homotransplant in dogs leads to its rejection in a manner similar to the host-versus-graft reaction of other tissues. The cells participating in the re-

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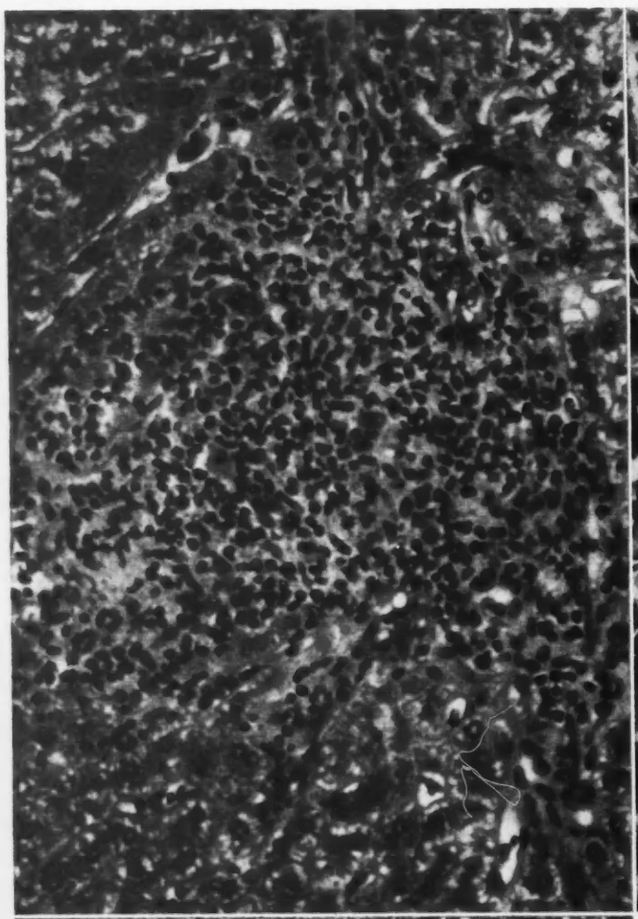

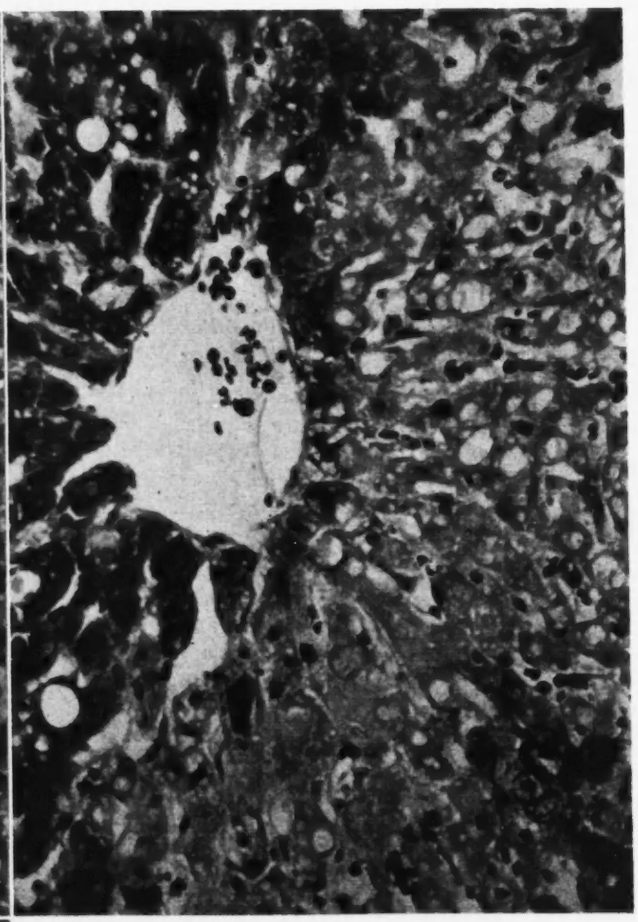

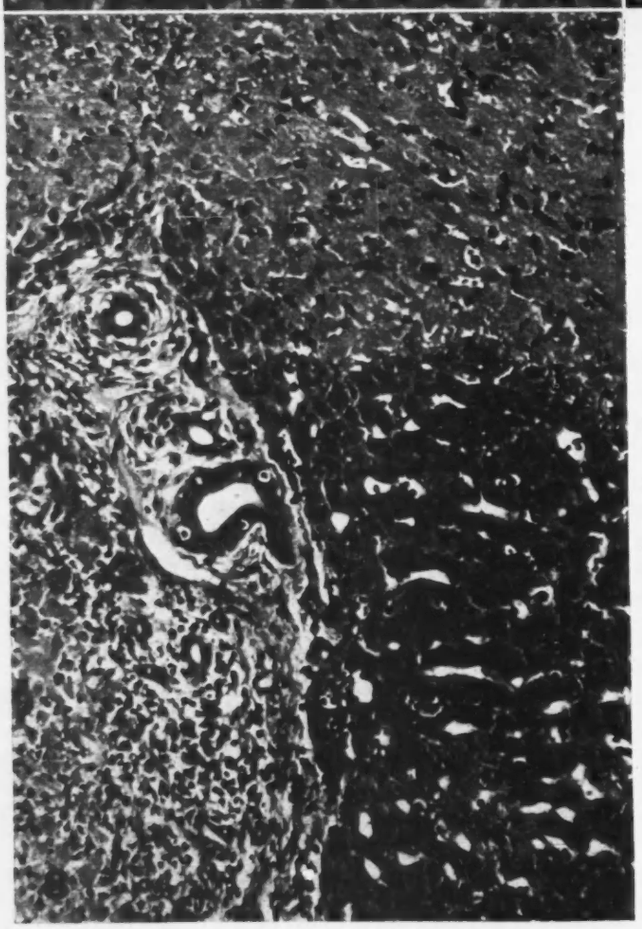

Fig. 6.—Rabbit. Four weekly intramuscular injections of a rabbit liver homogenate in Freund's adjuvant. Aggregation of mesenchymal cells in portal tract. This lesion may be attributed to the adjuvant alone. Hematoxylin and eosin, × 305.

Fig. 7.—Same procedure as Fig. 6. Total coagulative necrosis of paracentral portion of lobule. Note vacuolar degeneration on left of picture and relatively scanty cellular reaction. Hematoxylin and eosin, × 270.

Fig. 8.—Same procedure as Fig. 6. Ductular reaction in portal tract adjacent to area of coagulative necrosis of lobule (upper half of micrograph). The necrotic lesions seen in Figs. 7 and 8 are seen rarely. Hematoxylin and eosin, × 195.

jection were mainly lymphocytes and plasma cells. (These cells also proliferated in other organs normally containing reticuloendothelial elements. This reaction was thought to be related to the massive stimulation of the reticuloendothelial system by the antigens of the liver homograft. The possibility that transplanted mesenchymal cells in the graft attacked the host was considered to be unlikely.) Using rabbits as experimental animals, Leupold[38, 39] showed that injections of autolyzed rabbit liver tissue produced a specific liver injury. This was dependent upon the duration of autolysis (less than 48 hours) and on the pH of the autolysate. After 48 hours of autolysis, the injury became progressively more widespread. Autolysates of skin or kidney produced no injury to the liver.

When homologous liver homogenates *or* Freund's adjuvant were injected into *guinea-pigs* and hamsters, no necroses resulted. When these two sub-

stances were administered together in a single dose to the former species, necrosis of the liver parenchyma developed, particularly in young animals.[1] Most of the guinea-pigs died between 72 and 96 hours after the injection. The lesions showed no zonal distribution which was thought to exclude a direct toxic action of the liver-adjuvant mixture on the parenchyma. The lesions were interpreted as evidence of a *specific* antigen-antibody reaction, with the injected liver substance acting as an isoantigen. *Hamsters* showed a much slighter reticuloendothelial response than guinea-pigs, and necroses were less common.[1] *Mice* injected with a mixture of Freund's adjuvant and mouse liver homogenates developed no necrosis, but did develop amyloidosis and a proliferation of RE cells.[79] This reaction is identical to that produced by adjuvant alone.[37] To explain the difference between the response of guinea-pigs and hamsters on the one hand, and mice on the other, it was suggested that in the latter species the isoantigen-antibody interaction does not occur within cells, so that necrosis fails to develop.[79]

The experiments in guinea-pigs were repeated by Norkin *et al.*,[49] who found hyalin necroses in 50% of animals receiving Freund's adjuvant with a guinea-pig liver homogenate.

A further repetition of these experiments in guinea-pigs[19] showed that out of four animals injected, one developed necrosis and three had no lesions. These animals developed no delayed hypersensitivity to liver tissue when challenged with the homogenate into skin. Since the necroses were found near the surface of the liver, Field[19] suggested that they were ischemic in origin. This contention was based on the demonstration[15] that in rat livers blood-flow is normally distributed uniformly throughout the organ but at times the margin of the organ is excluded.

Jahiel and Koffler[31] demonstrated that when guinea-pigs were injected with normal liver homogenates with adjuvant or with homogenates of guinea-pig livers damaged by carbon tetrachloride with Freund's adjuvant, lesions developed which were identical. They consisted of multiple granulomas, predominantly epithelioid in character with occasional giant and plasma cells. The reticulum framework of the liver was preserved. Although scattered necrotic liver cells were seen surrounded by a leukocytic and histiocytic reaction, the massive necroses of Behar and Tal[1] were not demonstrated. Kupffer cells were often prominent and round cells increased in portal tracts.[31] Although the lesions were in no way different from those produced by the injection of adjuvant alone, there was a statistically significant increase of granulomas in those injected with liver plus adjuvant.

Since neither bacteria nor lipid could be demonstrated in the lesions, Jahiel and Koffler[31] dismissed the possibility that the lesions were due to a reactivation of a latent infection or embolization of components of the adjuvant. Since lesions were found as early as four days after injection, hypersensitivity to either Freund's adjuvant or to liver was considered unlikely. A direct toxic effect on liver cells could not be excluded.

We have repeated similar experiments in rabbits, rigidly excluding animals suffering from hepatic coccidiosis.[71] When Freund's adjuvant was administered with rabbit liver homogenates (Figs. 6, 7 and 8) or with rabbit bile (Figs. 9, 10 and 11), the lesions were similar to those in guinea-pigs as reported by Jahiel and Koffler.[31] However, approximately 25% of the animals developed more widespread necroses corresponding to those reported by Behar and Tal in young guinea-pigs[1] (Figs. 7, 8 and 11).

The Specificity of Experimental Iso-immune Liver Lesions

The specificity of the lesions was questioned for several reasons:

1. In some experiments the lesions caused by Freund's adjuvant alone and those produced by the addition to it of a potential liver isoantigen cannot be distinguished morphologically.[31, 49]

2. Degenerative changes of liver cells ("plant cell" and acidophilic degeneration) and necrosis near the surface of the liver can be found also in some normal guinea-pigs.[19]

3. Since in the original experiments of Behar and Tal[1] liver necroses developed as early as 72-98 hours after injection of the adjuvant-homogenate mixture, an isoimmune mechanism seems unlikely, at least in the early stages of the injury.[31]

4. The absence of delayed hypersensitivity in the skin of guinea-pigs injected with the adjuvant and liver speaks against an allergic mechanism. When a similar test is carried out in animals injected with a brain-adjuvant mixture, delayed hypersensitization can be demonstrated in almost 100% of the animals whether or not encephalitis is present.[19]

5. Homologous bile and Freund's adjuvant produce lesions which are indistinguishable from those produced by liver and adjuvant in rabbits.[71]

6. Injections of human-brain-adjuvant mixtures into guinea-pigs produce liver necroses and round cell infiltrations in portal tracts.[19]

7. Homologous liver or various liver fractions in Freund's adjuvant injected into guinea-pigs or hamsters produce a demyelinating and inflammatory brain lesion.[78]

8. Injections of homologous and autologous adrenal tissue suspended in Freund's adjuvant into guinea-pigs produce hepatic necroses[73] indistinguishable from those produced by Freund's adjuvant and liver homogenates[1] (Fig. 12).

9. Rat liver suspensions in Freund's adjuvant produce a nephrotic renal disease in rats. No liver lesions were reported in this experiment.[29]

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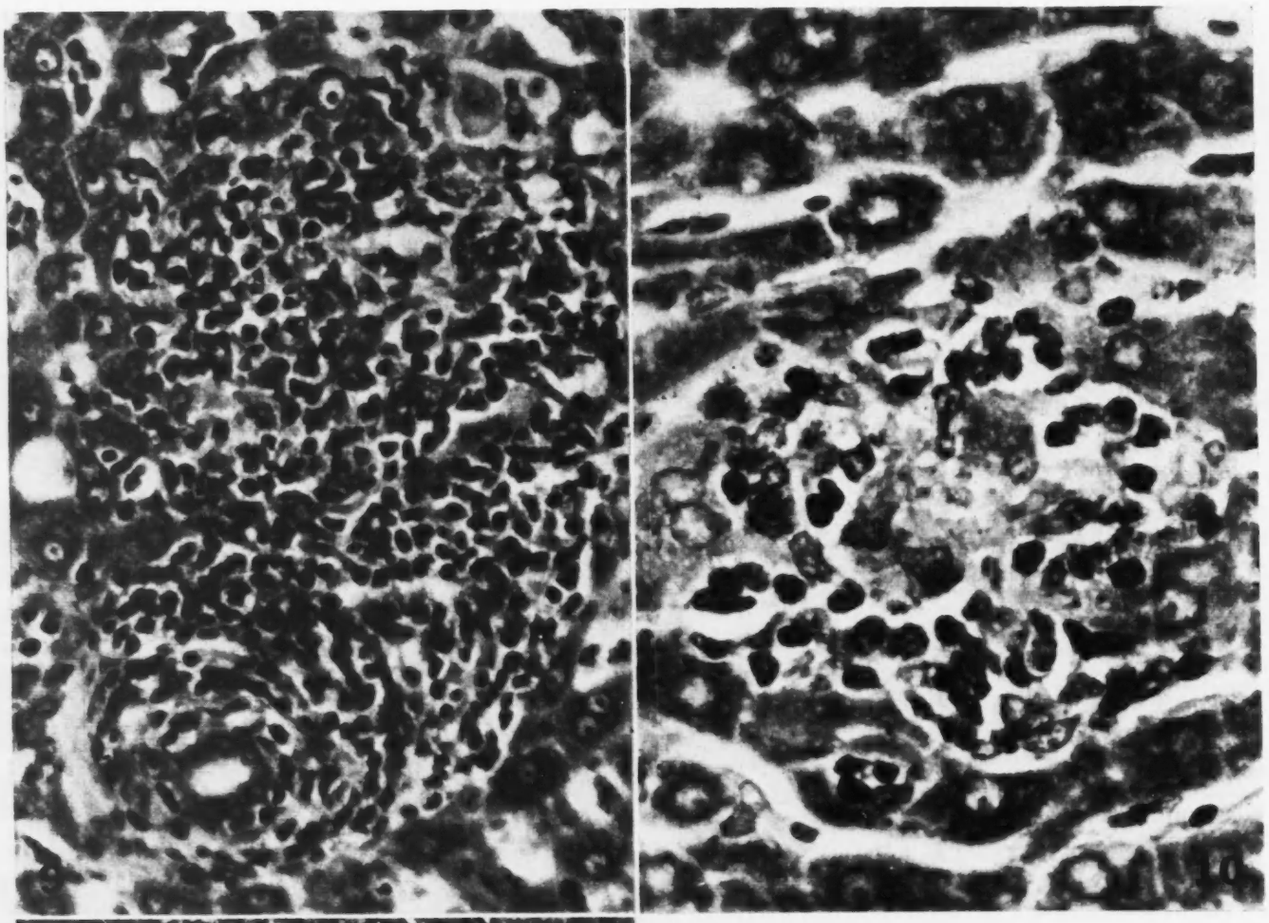

Fig. 9.—Rabbit. Four weekly intramuscular injection of pooled rabbit bile in Freund's adjuvant. Aggregation of mesenchymal cells in periportal area. This is attributed to the action of Freund's adjuvant. Compare with Figs. 5 and 6. Hematoxylin and eosin, × 468.

Fig. 10.—Same procedure as Fig. 9. Focal midzonal granulomatous lesion. This may be attributable to the action of the adjuvant. Azure eosin, × 910.

Fig. 11.—Same procedure as Fig. 9. Ductular reaction in portal tract adjacent to necrotic lobular lesion (upper margin of micrograph). This lesion was observed only rarely. Hematoxylin and eosin, × 305.

Conclusions

The evidence of an experimental isoimmune liver injury is at present inadequate and unconvincing for the following reasons:

1. Some normal animals have similar lesions.
2. Freund's adjuvant alone may at times induce lesions which are identical with those of the experimental model.
3. If the injury is allergic in origin, then it is not organ-specific, since it can be induced by other than liver antigens. This is supported by the finding that homologous liver antigens can induce lesions in organs other than the liver.
4. The rapidity with which lesions appear in some species speaks against an allergic mechanism. This does not exclude the possibility that hypersensitivity to either the potential antigen or to components of the adjuvant plays a role in the later phases of the development of the liver lesions.

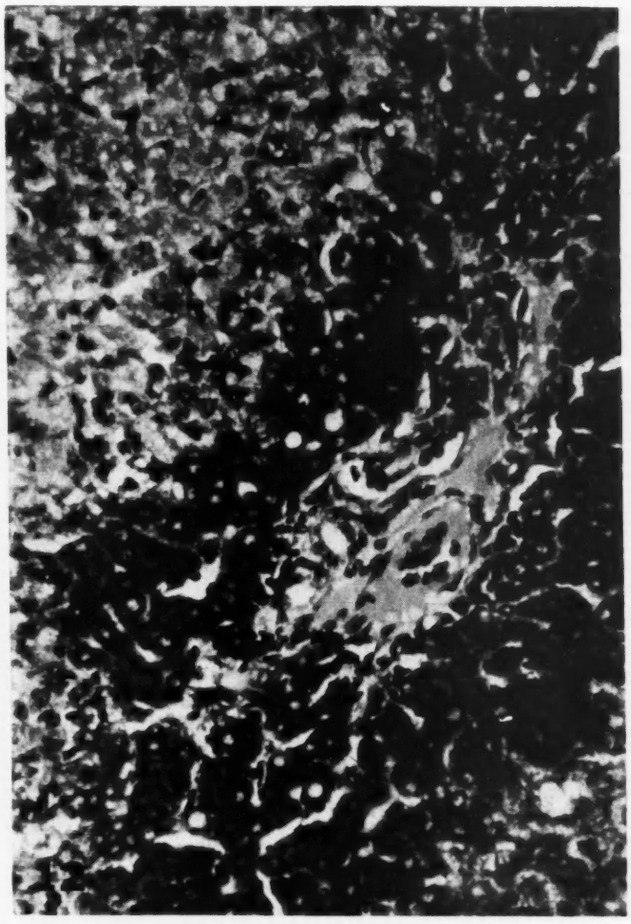

Fig. 12.—Guinea-pig. Four weekly intramuscular injections of a homogenate of one of its own adrenals in Freund's adjuvant. Midzonal coagulative necrosis of liver parenchyma (left upper corner) and intact parenchymal cells around portal tract. This lesion exemplifies the non-specific character of iso-immune anti-liver procedures. Azure eosin, × 250.

E. *Runting Syndrome and Secondary Disease*

The investigations of heteroimmune and isoimmune liver injury employed the method of rendering liver tissue antigenic either in an animal of another species or, by means of an adjuvant, in the same species. Such studies were in accord with those concepts of immunologic tissue injury which stressed the role of antigens in their evolution.

Burnet's clonal selection theory of acquired immunity[8] suggested that autoallergic injury may not be the result of change of a potential antigen to an autoantigen, but rather that it may be the result of a fundamental alteration of immunologically competent cells. If cells developed in the course of somatic mutation which lost the ability to distinguish between self and not-self, then such cells may interact with *normal* tissue components and lead to autoclasia. This generated the idea that mesenchymal cells may become autoaggressive.

Although it has been suggested that the experimental lesions of autoallergy, particularly experimental allergic encephalomyelitis, may be the result of such a self-destructive potential,[86] proof has been largely lacking and the evidence was circumstantial. The crux of the matter remained the question whether destruction of tissue in the various experiments of autoallergy precedes or follows the appearance of immunologically competent cells, particularly histiocytes, at the sites of lesions.

Medawar[46] laid the foundation for a new set of experiments of autoallergic tissue injury by pointing out that grafting of tissues is an act of parabiosis, in which the donor and recipient tissues become unequal partners. The possibility had to be considered that a transplant could mount a counter-attack against the recipient. It was found that a considerable percentage of newborn mice, rats and chicks[5, 66, 88] which were treated with adult homologous spleen cells, lymph node cells, buffy coat leukocytes or thymus cells became ill, failed to grow at a normal rate and died by four weeks of age. This disease became known as the runting syndrome or homologous disease. Hepatomegaly has been noted in runted mice,[12, 67] and liver lesions developed in them and in rabbits.[59, 68]

Changes were also found in the livers when chick embryos were inoculated with adult cock spleen cells[3] or with adult fowl blood cells.[4] The spleens and lymph nodes of all animals were also involved in the pathologic processes.

Since the runting syndrome is considered to be the result of an immunologic reaction of grafted mesenchymal cells against a tolerant host,[5, 66] this experimental model has to be taken into consideration in any discussion of immunologic liver injury.

When chick embryos were injected with rabbit spleen cells, bovine serum albumin or Hank's saline, no pathologic lesions resulted.[3] When they were injected with adult cock spleen cells, there was evidence of increased granulocytopoiesis and aggregation of reticulum cells in the liver. Areas of liver cell necrosis were occasionally surrounded by giant cells. Later the reticulum cell foci were transformed into lymphoid cells (with rare plasma cells) and a gradual return to normal structure.[3] When adult fowl blood cells were injected into chick embryos, the livers showed at first no necrosis. In chicks with chronic runt disease, who showed hypoplasia of lymphoid tissue, there was diffuse liver necrosis.[4] It was concluded that the lesions were the result of a donor-versus-host immune reaction mediated either by humoral (circulating) antibodies (because of the presence of plasma cells) or by "cell-bound antibodies" (because of the presence of primitive reticulum cells, blast cells and lymphocytes).

When newborn mice are injected with homologous liver cell suspensions no changes occur, but homologous spleen and lymph node cell suspensions induce runting.[68] A focal coagulative liver necrosis develops in these animals, mainly in subcapsular locations. There was little or no cellular reaction to this change. It was suggested that the lesions may be ischemic in origin owing to agglutination of the host red cells by antibodies formed by the donor cells. The possibility of infection was

also considered. No evidence, however, could be offered to account for the necrosis on the basis of an immunologic reaction between foreign cells and host tissue.

In the experiment using rabbits, homologous adult spleen cells were administered to the fetus *in utero*. The animals, after birth, developed the runting syndrome. Small focal areas of necrosis were noted in the livers of some. They showed no zonal distribution.[59] These lesions were identical with those produced in adult radiated animals injected subsequently with a suspension of adult homologous bone marrow ("secondary disease"). Although it is suggested that the lesions are the result of invasion and attack by donor cells, it is not known how this occurs and whether the injury is mediated by antibody.

Conclusions

We may conclude that hepatic lesions occur in immunologically defenceless animals (embryos or in radiation chimeras) challenged with homologous adult lymphoid cells. The mechanism of the liver injury is not known though it may be mediated by the injected cells either directly or by means of an anti-tissue antibody which they elaborate. These experiments have not confirmed unequivocally that lymphoid cells can produce liver injury by virtue of their *direct* anti-tissue aggressive activity.

F. *Experimental Autoallergic Liver Injury*

A model of this type of injury is at present not available.

G. *Suspected Autodestructive Processes in Human Liver Disease—Morphologic Considerations*

The morphologic evidence of autodestruction in human liver disease is scanty and largely circumstantial.

Some aspects of the nomenclature need to be clarified. The term "autoclasia" implies a process of autodestruction initiated by an immunologic response, i.e. by autoimmunization. The term "self-perpetuation" is not synonymous with autoclasia. Although it indicates an endogenous etiologic factor responsible for continuation and progression of an injury, it does not necessarily imply that this factor is immunologic in nature.[58]

1. An antibody in the sera of patients with biliary cirrhosis, malignant hepatitis and lupus erythematosus was shown, by immunohistochemical techniques, to have an affinity for the nuclei of parenchymal liver cells.[50, 51] Using the indirect method of Coons, an antibody was also found in the sera of patients with primary biliary cirrhosis and in one with obstruction of the common bile duct, with an affinity for the cytoplasm and nuclei of biliary epithelial cells and for bile within the lumina of bile ductules and ducts.[50, 51] It has been suggested that such antibodies *may be* concerned in self-perpetuation of these liver diseases.

2. Gamma-globulin-producing cells have been demonstrated in hepatic sinusoids and in fibrous connective tissue septa of livers of patients with various forms of hepatitis and postnecrotic cirrhosis.[13] It was suggested that these cells may be concerned with the causation and/or perpetuation of the liver injury.

3. The presence of "lymphoid" aggregates in the liver was thought to represent the marker of autoclasia.[40]

4. The presence of focal necrotic lesions associated with the presence of mesenchymal cells in the margins of regenerated liver lobules ("piecemeal necrosis") was considered to be the hallmark of a self-perpetuating injury in cirrhosis.[57]

CONCLUSIONS

1. The demonstration of gamma globulin antibodies in the sera of patients with various chronic liver diseases with an affinity for cells and nuclei of liver and biliary epithelial cells and of antibody-producing cells in other liver diseases was interpreted as possible evidence of an immunologic cause of self-perpetuation. The implication of these findings is that self-perpetuation may be the result of *circulating* autoantibody-endogenous antigen interactions. Three points speak against such a concept:

(a) Post-necrotic cirrhosis may develop in patients with agammaglobulinemia who lack cells capable of producing circulating antibodies.[28]

(b) There is no positive correlation between the presence and amount of circulating autoantibodies and the development of human or experimental autodestructive lesions.[62, 74-76]

(c) The experimental prototypes of liver injury produced by circulating antigen-antibody complexes lead rarely, if ever, to the development of cirrhosis in animals.[70]

2. The suggestion that aggregates of lymphoid cells in the liver represent a marker of autodestruction carries with it the connotation that such cells may be autoaggressive. The main support for this concept is derived from studies of the Simonsen phenomenon as exemplified by the liver injury in the runting syndrome.

(a) There is at present no agreement on the mechanism which is responsible for the liver injury in homologous disease. Although most investigators believe that the injury is immunologic in character, the possibility of mediation of such an injury by circulating antibodies has not been excluded.[3, 4, 59] Some have doubted the evidence that the injury is the result of a reaction between foreign cells and host liver tissue.[68]

(b) Aggregation of lymphoid cells in the liver may occur in circumstances which do not warrant the interpretation suggested by Mackay.[40] For example, the presence of such cells in the liver 24-

48 hours after ligation of the common bile duct of rabbits cannot be interpreted as evidence of autoclasia. In an immunopathologic sense this reaction may be interpreted as protective rather than destructive, e.g. that it represents an attempt to localize undesirable metabolites at the site of injury in portal tracts, thereby preventing their access to sites of systemic antibody production.

(c) Large lymphoid aggregates develop in the liver of animals following prolonged antigenic stimulation by a foreign protein (see Fig. 2 in the first part of this paper). These resemble closely the aggregates referred to by Mackay,[40] but they must be interpreted, in this instance, as a response to contact with an antigen rather than evidence of an autodestructive process.

3. Lastly, Popper's suggestion[57] that piece-meal necrosis may be the morphologic counterpart of self-perpetuation cannot at present be challenged, as long as it is stressed that self-perpetuation does not necessarily imply an immunologic mechanism.[58]

SUMMARY

We have set out to find the answer to two fundamental questions:

(1) Can one define the criteria of experimental immunologic liver injury in terms of its morphology and specificity?

(2) How do the prototypes of experimental immunologic injury support or negate the concept of autodestructive liver disease in the human?

We have concluded throughout this account that the morphologic criteria of immunologic liver injury are ill-defined. This is due to the limited capability of the liver to respond to injury. Neither cellular degeneration and necrosis nor a mesenchymal reaction are prerogatives of the immune response. One can only conclude that amongst the many causes of these forms of injury may be included those induced by immune mechanisms.

We can assert that circulating complexes of a nonspecific antigen and its homologous antibody may be injurious to the liver by whatever route they reach this organ. We may accept the evidence that circulating heterologous anti-liver as well as anti-erythrocyte and other anti-tissue antibodies may damage the liver. There is adequate evidence that homologous lymphoid cells may injure the liver of an immunologically defenseless animal. But we remain ignorant of the exact mechanisms which produce such an injury.

How can these thoughts be applied to human liver disease? In its broadest sense one can state that whenever parenchymal cell degenerations, necrosis and mesenchymal cell infiltrations are found in the liver, particularly when they occur jointly, immune processes may be implicated. We can go further. Whenever such lesions are found in the liver in conjunction with a known or suspected *intravascular* immunologic reaction (circulating antigen and antibody) the lesions may be accepted as probably being of allergic etiology. Examples of such lesions are those which are associated with sulfonamide[48] and penicillin[87] hypersensitivity.

Finally, we must conclude that there is at present no convincing human or experimental morphologic evidence available to substantiate the implication of autoclasia as a mechanism of initiation or of self-perpetuation of liver injury. Nevertheless, autoimmunization as a possible contributory factor to the development of liver disease can not be entirely ruled out. The burden of providing the necessary proof rests with the experimental immunopathologist.

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THE EPIDEMIOLOGY OF TUBERCULOSIS IN ONTARIO, 1960

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"Tuberculosis detection—and therefore tuberculosis control—is no better than its bookkeeping."†

INTRODUCTION

THE Ontario Tuberculosis Register commenced its work on January 1, 1960. The need to establish suitable machinery to provide an accurate picture of the problems of tuberculosis had been felt for many years. After the advent of antimicrobial treatment, deaths from tuberculosis became uncommon and the mortality rate ceased to be an index of practical importance. More attention had to be given to morbidity. The task of obtaining reliable morbidity data would at first sight appear simple because tuberculosis is a notifiable disease. However, the duty of notification is not always carried out: for instance, in 1960, 40% of active cases admitted for the first time to sanatoria were not reported by the medical officers of health to the Ontario Department of Health.

Reports from sanatoria about the admission of cases of tuberculosis were in previous years used as an index of morbidity. This is not reliable because only 80% of the active cases of tuberculosis are admitted at present, and not all the cases admitted with a label "tuberculosis" have active disease; many are inactive and are admitted for treatment of other conditions. A large group are admitted for assessment of activity—cases of so-called "undetermined activity".

Among other sources of information about active cases are the positive reports on bacteriological examinations for tubercle bacilli carried out by provincial laboratories, and notifications from the Registrar General concerning deaths from tuberculosis.

All the information derived from the various sources and relating to one individual is recorded on a special card bearing a register number which is unique for that particular patient. This step has gone a long way to close the gap between the number of forms received and the actual number of patients to which they refer.

Tuberculosis is still a dangerous disease. Thanks to the efforts in the field of prevention and treatment over many decades, and to the high standard of living in Ontario, over 80% of the population are negative tuberculin reactors; apparently they have not been exposed to tuberculous infection. While there are appreciable risks arising from infection with tubercle bacilli, there are also certain benefits—an individual who has successfully resisted infection develops a degree of immunity to further exposure; this is reflected by a general reluctance to employ tuberculin negative (uninfected) people to care for tuberculous patients. The sputum-positive case of tuberculosis is a great danger to a community that consists of people previously uninfected. This has brought us to the somewhat paradoxical situation in which, despite the decline in tuberculosis, it is necessary to strengthen, not weaken, the control exercised over actual and potential sources of infection.

The year 1960 was the first year of operation of the Register, and in many of the analyses presented here the information is available for the majority, but not for all the cases. It is hoped that this report will act as a stimulus to all concerned to provide complete and accurate information on all patients suffering from tuberculosis.

MORTALITY

During 1960, 157 deaths attributed to tuberculosis were reported by the Registrar General; this

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†The Arden House Conference on Tuberculosis, November 1959.

TABLE I.—TUBERCULOSIS MORTALITY—AGE AT DEATH ONTARIO, 1960

Age groups	*Deaths*	*Total deaths*
0 - 4	3	
5 - 9	—	
10 - 14	—	
15 - 19	3	
20 - 29	6	
30 - 39	10	
40 - 49	15	
50 - 59	24	
60 - 69	42	
70+	54	157

TABLE II.—TUBERCULOSIS MORTALITY—SITE AND TYPE OF DISEASE—ONTARIO, 1960

Type of disease	*Deaths*
Pulmonary tuberculosis	132
Tuberculous meningitis	6
Genitourinary tuberculosis	5
Bone and joint tuberculosis	3
Tuberculous peritonitis	2
Other tuberculous conditions: empyema, miliary and polyserositis	3
No information (site and type of disease not specified)	6
	157

is a mortality rate of 2.6 per 100,000, the lowest ever recorded in Ontario.

Deaths attributed to tuberculosis include not only the patients who died from active disease but also those dying from conditions such as pulmonary fibrosis and cor pulmonale, in whom tuberculosis was thought to be the process initiating subsequent fibrosis and heart failure. Actually, at the time of death only 106 (67.5%) were suffering from active tuberculosis (75 of these active cases had bacilli in their sputa).

Of the 157 deaths, 109 (69.4%) occurred in males and 48 in females. The age distribution of these 157 patients is shown in Table I.

The predominance of older persons is obvious; 96 (61%) of the 157 deaths occurred in people over 60. The high mortality rate in older people is probably accounted for by several factors: longer duration of the disease, more extensive fibrosis, or less response to treatment, etc. They also have a much higher incidence of serious associated disease. That this is important is well shown by the study of the records of these cases: two of them had bronchogenic carcinoma; two carcinoma of the stomach; one leukemia; one Hodgkin's disease; three recent coronary thrombosis; and two cerebral thrombosis. This list of fatal disorders suggests that some of these deaths would perhaps be more correctly ascribed to a non-tuberculous cause.

It is also of interest that at least 22 of these 157 patients had pulmonary fibrosis and cor pulmonale; the fact that in four of them silicosis was mentioned suggests that tuberculosis was not the only etiological factor in the causation of pulmonary fibrosis in these patients.

Table II shows the types of tuberculous disease in these 157 cases.

The predominance of pulmonary tuberculosis (87.4% of deaths with type of disease recorded) is practically the same as that seen in tuberculosis morbidity (Table IV).

It is quite clear from the relative infrequency of deaths from tuberculosis that tuberculosis mortality is no longer a valuable epidemiology index. It is probably true today that, except for the elderly, the chance of anyone's dying from active disease is remote. Some of the deaths, particularly those in the younger age groups, may well reflect a breakdown in our diagnostic and preventive services. Perhaps a special committee should be formed to investigate deaths from tuberculosis in much the same way as maternal deaths are investigated.

MORBIDITY

Two thousand and thirty (2030) persons were recorded as having developed active tuberculosis during 1960, giving a morbidity rate of 33.3 per 100,000, or one case for each 3000 people. These included both patients with new disease and those with arrested disease which had broken down. Tubercle bacilli were isolated in 1911 (58.7%) of the 2030 cases.

Age and Sex Distribution

Table III shows that of the 2006 cases of active tuberculosis for whom information regarding sex

TABLE III.—AGE-SPECIFIC TUBERCULOSIS MORBIDITY AMONG MALES AND FEMALES—ONTARIO, 1960

	Males			*Females*		
Age group	*Number with active tuberculosis*	*Total population*	*Rate per 100,000*	*Number with active tuberculosis*	*Total population*	*Rate per 100,000*
0 - 9	74	703,900	10.5	67	674,100	9.9
10 - 19	54	494,500	10.9	58	470,500	12.3
20 - 29	148	418,700	35.3	139	401,500	34.6
30 - 39	176	454,500	38.7	143	452,500	31.6
40 - 49	151	382,900	39.4	96	372,900	25.7
50 - 59	187	285,800	65.4	65	276,000	23.6
60 - 69	190	186,000	102.2	49	201,400	24.3
70 - 79	105	108,800	96.5	33	129,600	25.5
80 - 89	29	29,100	99.7	19	40,200	47.3
90+	3	2,300	130.4	4	3,800	105.3
No information	118	—	—	98	—	—
	1,235	3,066,500	40.2	771	3,022,500	25.5

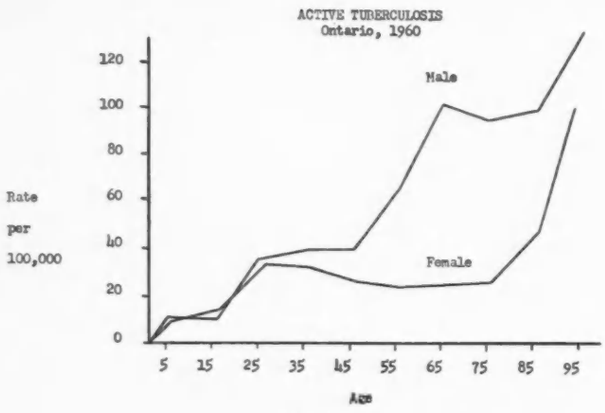

Fig. 1

was available, 1235 (61.6%) were males and 771 (38.4%) were females. This table and Fig. 1 reveal that, among males, tuberculosis is relatively much more common after the age of 45. The rates are noticeably higher in later life. Thus, the older the man the more likely he is to develop active tuberculosis. In the first three decades of life the morbidity rate is very similar in both sexes. The rate in females at age 80 and over shows a pronounced rise; however, in this age group the actual number of cases is very small.

Site and Type of Disease

Table IV shows the division of active cases according to site and type of disease. Over 88% of the cases were of pulmonary tuberculosis. Bacteriological confirmation was available in 892 (54.7%) of the 1632 pulmonary, and in 121 (56.3%) of the 215 extra-pulmonary cases. These figures emphasize the great value of bacteriological examinations and leave no doubt that the search for tubercle bacilli should be done frequently.

It is of interest that the types of tuberculosis which develop soon after the primary infection are relatively uncommon. Because tuberculous meningitis was invariably fatal in the pre-antibiotic era, a justifiable comparison can be drawn between the present morbidity and the mortality from tuberculous meningitis in previous years (Table V).

TABLE IV.—ACTIVE TUBERCULOSIS—SITE AND TYPE OF DISEASE*—ONTARIO, 1960

Pulmonary tuberculosis		*Extra-pulmonary tuberculosis*	
Post-primary pulmonary tuberculosis	1367	Skin	4
Primary tuberculosis	134	Bone and joint	30
Pleural effusion	63	Thoracic	8
Other	68	Lymph gland	46
		Alimentary	9
		Genito-urinary	101
		Central nervous system (meningitis)	13
		Adrenals	1
		Multiple systems	3
Total	1632	Total	215

*In 183 cases information relating to the site and type of disease was not available. They were all cases reported in the first months of 1960 when routine enquiries about positive bacteriological reports were not made.

TABLE V.—TUBERCULOUS MENINGITIS ONTARIO 1920, 1940, 1960

Year	*1920 Mortality*	*1940 Mortality*	*1960 Morbidity*
Number of cases	125	59	13
Rate per 100,000	4.3	1.6	0.2

Of the 13 cases of meningitis recorded in 1960, only three were inpatients under the age of 20 and the remainder were between 20 and 50.

Pleurisy with effusion is also an early complication of tuberculosis, the majority of cases occurring within the first nine months after primary infection. Sixty-three cases of this condition were recorded, giving a rate for 1960 of 1.0 per 100,000. While there are no comparable data for previous years, figures for cases of pleural effusion treated in sanatoria are available. They undoubtedly underestimate the incidence of pleural effusion as many cases must have been treated at home. Nevertheless, in 1955 there were 120 cases of pleural effusion admitted to sanatoria, giving an incidence of 2.3 per 100,000; thus, in the last five years there has been a decline in the incidence of this condition from over 2.3 to 1.0 per 100,000.

The number of cases of primary tuberculosis is still relatively large—134. Judging by sanatoria statistics, there has been no appreciable decline in their number over the past few years. This is undoubtedly due to the fact that with the extension of the school tuberculin surveys, more thorough contact examinations, and the availability of sanatorium beds, more of these cases are being reported and treated.

Post-Primary Pulmonary Tuberculosis

Pulmonary tuberculosis of "reinfection", "adult" or "chonic" type has always constituted the main problem in tuberculosis. It is not only the most common form but, for practical purposes, is also the only form of the disease that is infectious. This type of disease accounted for 1367 cases (74%) of the active cases (Table IV).

Table VI shows the extent of the disease in these 1367 cases, according to the standards of the National Tuberculosis Association (United States).

The "moderately advanced" group is the largest, constituting 44.8% of the cases. The "far advanced" group accounts for a little more than one-quarter (26.1%) of the patients. It is of interest to note that the corresponding proportion of cases of far-advanced pulmonary tuberculosis admitted to sanatoria in 1955 was 28.5%. Thus, apparently little progress has been made in the last five years

TABLE VI.—PULMONARY TUBERCULOSIS "REINFECTION" TYPE—EXTENT OF DISEASE—ONTARIO, 1960

Extent of disease	*Number of cases*	*Percentage*
Far advanced	357	26.1
Moderately advanced	613	44.8
Minimal	397	29.1
	1367	100.0

TABLE VII.—RISK OF PULMONARY TUBERCULOSIS IN THE TUBERCULIN-POSITIVE INDIVIDUALS—ONTARIO, 1960

A	*B*	*C**	*D*	*E*	*F*
Age group	*Population*	*Per cent tbn.-pos.*	*Estimated number tbn.-pos.*	*Pulmonary tuberculosis*	*Established rate per 100,000 tbn.-pos.*
			Males		
0 - 4	371,300	0.5	1,856	1	54
5 - 9	332,600	1.0	3,326	2	60
10 - 14	279,000	2.8	7,812	5	64
15 - 19	215,500	5.4	11,637	27	232
20 - 29	418,700	16.8	70,341	117	166
30 - 39	454,500	37.8	171,801	141	82
40 - 49	382,900	45.9	175,751	132	75
50 - 59	285,800	51.1	146,043	173	118
60 - 69	186,000	52.6	97,836	177	181
70+	140,200	38.7	54,257	127	234
			Females		
0 - 4	353,700	0.4	1,414	3	212
5 - 9	320,400	1.1	3,524	6	170
10 - 14	265,800	2.6	6,190	10	145
15 - 19	204,700	5.0	10,235	31	303
20 - 29	401,500	13.1	52,596	98	186
30 - 39	452,500	27.7	125,342	108	86
40 - 49	372,900	32.1	119,700	84	70
50 - 59	276,000	37.1	102,396	50	49
60 - 69	201,400	36.3	73,108	42	57
70+	173,600	31.0	53,816	46	85

*Based on 177,259 consecutive Mantoux tests carried out in Ontario between 1958 - 1960.

in the diagnosis of pulmonary tuberculosis before it becomes far advanced.

Many years ago in Ontario post-primary pulmonary tuberculosis was predominantly a disease of adolescents and young adults. This is still true in many parts of the world today. The present relative frequency of this disease among older age groups here may be due simply to the fact that the vast majority of younger people are not infected with tubercle bacilli. In the last few years extensive tuberculin surveys have been carried out in this province, and it is possible now to form a fairly accurate idea about the overall frequency of positive tuberculin reactions in various age groups (Table VII, column C, and Fig. 2). The incidence of tuberculous infection, as revealed by positive reaction, is relatively low in childhood, rises rapidly through the first half of adult life and actually falls among the older segments of the population. There is good reason to think that the results of tuberculin testing underestimate the incidence of infection among the elderly, who for some reason show a diminished reaction to the customary dose of five tuberculin units.

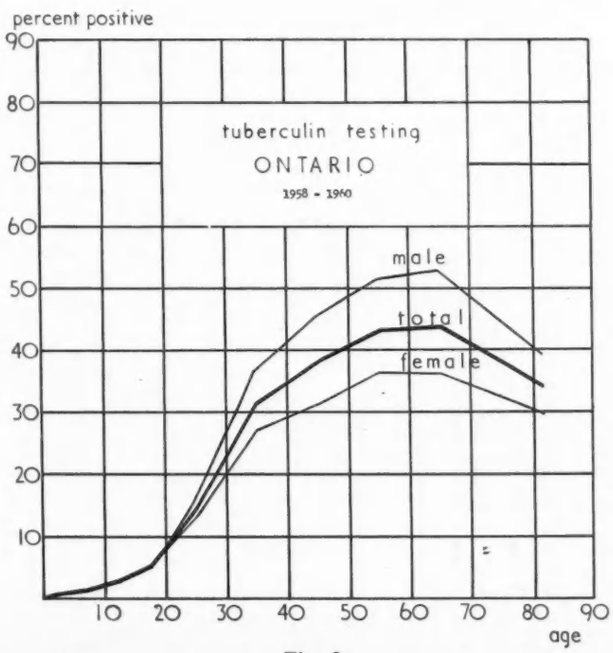

Fig. 2

In Table VII the incidence of active post-primary pulmonary tuberculosis is expressed in relation to the estimated number of tuberculin-positive individuals in each age group.

The results of this analysis indicate that there has been no fundamental change in the nature of pulmonary tuberculosis. Among infected persons, active pulmonary tuberculosis is still most likely to develop in those between the ages of 15 and 30 years. Adolescent tuberculin-positive girls still show the highest incidence of pulmonary tuberculosis. The fact that so little tuberculosis is actually seen among these younger women is merely an expression of the low infection rate experienced by this group. In perusing this table, one must keep in mind the likelihood that the results of tuberculin testing among the elderly are apt to under-estimate the true infection rate. Thus the risk of developing the disease in the elderly, shown here, is probably somewhat exaggerated. It is also possible that the risk figures for children under ten are also exaggerated, but for a different reason; "reinfection type" of pulmonary tuberculosis is very uncommon in this age group, and it is likely that some of these children were suffering from primary tuberculosis.

It should be repeated that this analysis deals with "re-infection" type of tuberculosis. The risk of

developing other types of disease, notably those due to hematogenous dissemination attendant upon infection in childhood, and particularly in infancy, is very high indeed.

Because the tuberculin status of an increasing number of people is being established, the results of this analysis are of considerable practical importance. They show that, among the known positive reactors, the most important groups to be kept under supervision are young women and men between the ages of 15 and 30.

Management of Active Tuberculosis

For 1960 it is possible to give only an outline of the picture of the management of tuberculosis in Ontario. By the end of 1960, 1611 of the 2030 active cases had been admitted to the 12 Ontario sanatoria; 11 to sanatoria outside Ontario, and 36 to other institutions with tuberculosis units. Thus the total number of patients undergoing institutional therapy was 1658.

It is not possible to gather complete information about all the remaining 372 patients, 85% of whom had pulmonary tuberculosis. It was found, however, that 27 had died (all outside of sanatorium), seven had left Ontario, three were found to have been infected with unclassified mycobacteria (not tubercle bacilli), and in one the positive bacteriological report was considered to have been a laboratory error. The group of 27 persons who had active tuberculosis during a terminal illness is of some importance; while most of these people did not die primarily of tuberculosis, there remains the likelihood that many of them were an unsuspected source of infection for a long period before death.

Knowledge was available about the actual or intended management of 164 of the remaining cases. This is shown in Table VIII.

In Table VIII, it can be seen that only 78 (47.6%) of the 164 cases were treated with antimicrobial agents at home or in a general hospital. In 15 (9.1%) of these cases there apparently was some doubt as to the activity, and they are being supervised and investigated further, but not treated. Finally, there were 71 (43.3%) "uncooperative" patients for whom sanatorium admission was recommended but who had not been admitted.

Thus the proportion of active cases not admitted to sanatorium is quite appreciable—somewhere in the region of one in every five. Of those not admitted, possibly only one-half are receiving antimicrobial treatment.

TABLE VIII.—MANAGEMENT OF ACTIVE TUBERCULOSIS CASES NOT ADMITTED TO SANATORIUM—ONTARIO, 1960

Management	*Number of cases*	*Percentage*
Treated with antimicrobial agents	78	47.6
Under supervision or investigation, but not treated	15	9.1
Recommended for admission to sanatorium, but not admitted	71	43.3
	164	100.0

The number of cases of active tuberculosis not treated in sanatorium is likely to increase in the future. It is of paramount importance that these patients should receive adequate and well-supervised ambulatory treatment with antimicrobial drugs. The duty of public health agencies and chest clinics in this connection extends beyond recommending sanatorium admission for the patient and, should he refuse, in merely labelling him "uncooperative". Every effort should be made either to require such a patient to enter a sanatorium or to treat him on an ambulatory basis, in the realization that while such treatment is not as satisfactory as sanatorium treatment, it is infinitely better than no treatment at all.

Method of Detection

The results of a study of the agency responsible for diagnosis in a sample of 724 consecutive admissions to sanatoria with active tuberculosis are shown in Table IX.

The chest clinics were responsible for the diagnosis of over one-quarter of active cases. This figure is high when one considers that the chest clinic service in many parts of Ontario is not as well developed as it is in larger population areas. Undoubtedly, with the further expansion of the chest clinic services, which appear imminent in view of the profound changes in the management of tuberculosis, the clinics are likely to contribute to the diagnosis of an even larger proportion of cases than they did in 1960.

The contribution of the general hospitals was also considerable (22.8%); this is not surprising, as tuberculosis often causes symptoms severe enough to warrant hospitalization. Private physicians were directly responsible for the diagnosis of 21.7% of the cases; this indicates that, contrary to the opinion of some, general physicians are amply conscious of the problem of tuberculosis.

The mass surveys were responsible for the diagnosis of 12.4% and the hospital admission program for 7.4% of active cases; these are significant contributions.

Considering its rather limited scope and cost, the jail program, with its over 2% contribution, constitutes a very rewarding case-finding project.

TABLE IX.—METHOD OF DETECTION OF ACTIVE CASES OF TUBERCULOSIS (SAMPLE OF 724 CONSECUTIVE CASES) ONTARIO, 1960

Source of detection	*Total cases*	
	Number	*Per cent*
Chest clinic	186	25.7
General hospital	165	22.8
Private physicians	157	21.7
Mass surveys:		
industrial	32	4.4
community	58	8.0
Hospital admission	54	7.4
Pre-employment	10	1.4
Jail program	15	2.1
Other	47	6.5
	724	100.0

Actually, the case-finding rate in jail surveys is approximately ten times that in community surveys.

Tuberculosis in the Main Population Groups

Some years ago it was noted that there might be advantages in considering the problem of tuberculosis in Ontario in different population groups, e.g. Canadian-born, Indians and foreign-born. This differentiation was found to be very useful in considering the incidence of tuberculous infection.

A study of the morbidity rates in these groups is rendered difficult by the fact that there is no reliable up-to-date information on the relative contribution of these groups to the total population.

"The Census of Indians in Canada, 1959" shows that 42,668 Indians were counted in the province of Ontario. This represents some 0.7% of the total population. With the foreign-born people the latest information relates to the 1951 census, at which time 18.5% of the population of this province had been born outside Canada. It is probable that in the last decade this proportion increased appreciably.

Table X shows the incidence of active tuberculosis in the three main groups of the population of Ontario.

TABLE X.—ACTIVE TUBERCULOSIS IN THE THREE MAIN GROUPS OF POPULATION—ONTARIO, 1960

Group	*Number of cases*	*Percentage*
Canadian-born (excluding Indians)	873	56.2
Foreign-born	560	36.1
Indians	119	7.7
	1552	100.0

In 429 patients no information on population grouping was available; 49 cases from outside Ontario were excluded.

Indians contributed some 7.7% of the active cases of tuberculosis; that is, more than ten times what they could be expected to contribute from their proportion in the population, 0.7%. It is likely that this figure of 7.7% is still an underestimate, as there is reason to believe that a number of cases of tuberculosis among Indians were not reported to the Register in 1960.

There is another aspect of the tuberculosis picture among Indians which gives rise to concern. An attempt has been made to divide the active cases into those which were likely the result of recent infection, and those in which no conclusion is possible as to the time of infection. The "recently infected" cases consist of primary tuberculosis, pleurisy with effusion, meningitis, and cervical adenitis; these forms tend to occur early in the natural history of tuberculosis. Of 119 Indians with active tuberculosis, 30 (25.2%) fall into this category. This is about twice as many as in the case of the non-Indian population, where there were 185 (12.9%) "recently infected" cases out of 1433 active cases. While the figures are small and this type of analysis would have to be extended before any firm conclusions could be reached, it tends to indicate that early forms of tuberculosis are more common among Indians. This suggests that new infections in that group of the population have not yet been controlled to the same extent as in the white population.

Bearing in mind the 1951 census figures, the proportion of 36.1% of the cases of tuberculosis contributed by foreign-born people is appreciably higher than anticipated from their contribution to the population. However, analysis of the present situation in this regard has to await the publication of the results of the 1961 census.

Geographical Distribution of Active Tuberculosis in Ontario

Many counties and districts in Ontario have a small population and in 1960 had few cases of tuberculosis. It would therefore be unwise to devote too much attention to the differences between such counties, as these may be due to chance.

In order to recruit larger and more valid numbers the counties were grouped into several divisions, designed by the Department of Economics of Ontario. These ten main divisions are as follows:

Eastern Ontario—Carleton, Dundas, Frontenac, Glengarry, Grenville, Lanark, Leeds, Prescott, Renfrew, Russell, Stormont.

Lake Ontario—Durham, Haliburton, Hastings, Lennox and Addington, Northumberland, Peterborough, Prince Edward, Victoria.

Metropolitan—Halton, Ontario, Peel, York.

Niagara—Brant, Haldimand, Lincoln, Welland, Wentworth.

Lake Erie—Elgin, Middlesex, Norfolk, Oxford.

Lake St. Clair—Essex, Kent, Lambton.

Upper Grand River—Huron, Perth, Waterloo, Wellington.

Georgian Bay—Bruce, Dufferin, Grey, Muskoka, Parry Sound, Simcoe.

Northeastern Ontario—Algoma, Cochrane, Manitoulin, Nipissing, Sudbury, Timiskaming.

Lakehead (Northwestern Ontario)—Kenora, Rainy River, Thunder Bay.

Table XI shows the incidence of active tuberculosis in these divisions of Ontario. It will be seen that the highest morbidity rate was found to be in Northwestern Ontario—62.0 per 100,000; the lowest, 16.5 per 100,000, was in the Upper Grand River area. When, however, the Indians are excluded, Northeastern Ontario becomes by far the highest incidence area, with a rate of 41.4 per 100,000, followed by Metropolitan and Eastern Ontario divisions, with rates of 33.4 and 32.3 respectively.

Distribution of Active Cases in Cities and Rural Areas

Table XII shows the incidence of active disease in cities of various sizes, and in small towns and rural areas.

TABLE XI.—INCIDENCE OF ACTIVE TUBERCULOSIS IN VARIOUS DIVISIONS OF ONTARIO—ONTARIO, 1960

Division	(Estimated) population	Cases of active tuberculosis			Rate per 100,000	
		Total	Indians	Whites	Total	Excluding Indians
Eastern Ontario	758,600	248	3	245	32.7	32.3
Lake Ontario	332,770	67	—	67	20.1	20.1
Metropolitan	2,015,320	679	7	672	33.7	33.4
Niagara	748,970	216	8	208	28.8	27.7
Lake Erie	397,220	83	2	81	20.9	20.4
Lake St. Clair	450,860	103	2	101	22.8	22.4
Upper Grand River	368,770	61	1	60	16.5	16.2
Georgian Bay	314,580	56	1	55	17.8	17.5
Northwestern Ontario	485,940	218	17	201	44.9	41.4
Lakehead, Northwestern Ontario	215,970	134	71	63	62.0	29.1
Outside Ontario	—	49	—	—	—	—
No official residence	—	116	—	—	—	—
	6,089,000	2,030	(112)	(1,753)	33.3	—

There are no significant differences between the cities of various sizes. However, the incidence in small towns and rural areas is 23.8 per 100,000, whereas in cities, and in towns with populations higher than 5000, the incidence is of a higher order. It is possible that this lower incidence in rural areas is to some extent due to poorer diagnostic facilities; however, it is likely that tuberculosis is somewhat less prevalent in these areas.

TABLE XII.—TUBERCULOSIS IN CITIES, TOWNS AND RURAL AREAS—ONTARIO, 1960

Areas	Population*	Active cases†	Percentage per 100,000
Cities over 100,000 population	2,304,830	859	37.3
Cities and towns 20,000-100,000	1,050,560	356	33.9
Cities and towns 5,000-20,000	445,364	172	38.6
Small towns and rural areas	2,007,992	478	23.8

*Population based on Municipal Directory, 1961.
†Cases not included: 49—outside Ontario.
116—no information on residence.

Tuberculosis in Large Cities

Table XIII shows the incidence of active tuberculosis in cities of over 100,000.

Of the large cities in Ontario, Windsor showed the highest incidence rate, 46.5 per 100,000, followed by Toronto with 39.6 per 100,000. The lowest incidence was seen in London, 24.0 per 100,000.

It is possible that these differences between the large cities could be accounted for by the differences in the composition of the population, e.g. the ratio of Canadian-born to foreign-born people. However, there are no current data in this field, and when the results of the 1961 census become available this analysis may be extended.

TABLE XIII.—TUBERCULOSIS IN CITIES OF OVER 100,000 POPULATION—ONTARIO, 1960

Cities of over 100,000 population	Population*	Active cases reported, 1960	Rate per 100,000
Toronto (Metropolitan area)	1,513,790	599	39.6
Hamilton	261,114	77	29.5
Ottawa	255,608	91	35.6
London	158,158	38	24.0
Windsor	116,160	54	46.5
	2,304,830	859	37.3

*Based on the Municipal Directory, 1961.

Bacterial Resistance

There is no complete agreement as to the clinical significance of resistance studies on tubercle bacilli. This is particularly true with regard to partial resistance; some authorities regard it as a grave occurrence closely anteceding the development of full resistance, while others feel less sure of its importance. Most would agree that a patient with tubercle bacilli resistant to one of the principal drugs, while susceptible to the remaining two, is seldom a clinical problem. With an eye to the future control of tuberculosis, however, the rapid emergence of drug resistant strains in many countries is fraught with great danger. The present treatment of tuberculosis may become useless before new effective drugs are introduced.

There is no clear-cut solution to the vital task of avoiding the development of resistant strains. Nevertheless, clinical experience dictates that part, if not all, of this problem could be solved by the strictest possible adherence to the well-established rules of treatment, which include the carefully supervised continuous use of combined chemotherapy for a sufficiently prolonged period.

Of the 2030 active cases of tuberculosis recorded in the Register in 1960, the results of susceptibility studies relating to the three main drugs are available for 332. According to these records, in 183 of the 332 patients the studies were carried out prior to, or at the beginning of, the first course of antimicrobial treatment; the remaining 149 patients had been treated previously.

Tables XIV and XV show the results obtained in the study of the first of these groups:

These findings indicate that while bacterial resistance seldom precludes successful treatment with two of the three main drugs, the fact remains that over a quarter of these untreated patients showed some degree of resistance to at least one drug.

TABLE XIV.—SUSCEPTIBILITY STUDIES ON CULTURES OBTAINED FROM 183 CASES WITHOUT A RECORD OF PREVIOUS TREATMENT—ONTARIO, 1960

	Reactions in cases studied	*Percentage of total*
*Resistant to three drugs		
—fully	—	—
—partially to all	1	0.5
Resistant to two drugs		
—fully to 2	—	—
—fully to 1, partially to 1	6	3.2
—partially to 2	8	4.3
Resistant to one drug		
—fully	12	6.6
—partially	23	12.6
Fully susceptible to three drugs	133	72.8
	183	100.0

*Drugs referred to in these and succeeding tables are streptomycin, PAS and INH.

The results of susceptibility studies to individual drugs are of interest, as shown in Table XV.

Streptomycin is the drug to which most of the resistance is encountered, and over one-quarter of these patients showed some degree of resistance to this drug. It is encouraging to note that none of the patients showed full resistance to isoniazid, and only two cases were found to be partially resistant to it; 15 showed some degree of resistance to PAS.

The results of resistance tests on the 149 patients who were previously treated look quite different and are presented in Tables XVI and XVII.

Less than one-half of these patients, who had received previous treatment, were susceptible to the three main drugs used in the treatment of tuberculosis. Close to one in five showed full resistance to at least two drugs, probably precluding the satisfactory use of standard chemotherapy.

Comparison of the results obtained in these two groups of patients is of importance in the assessment of the incidence of infection with resistant bacilli in the general population. Some of the cases in the first group, without previous treatment, probably had disease which was the direct result of infection acquired long ago, in the pre-antibiotic era; thus, the incidence of resistant bacilli in this group very likely underestimates the present problem of infection with resistant organisms in the community. On the other hand, the incidence of resistant organisms in the second group has the reverse effect, as in some institutions resistance studies are not done routinely, but only on cultures from patients who fail to improve on treatment.

TABLE XV.—SUSCEPTIBILITY TO INDIVIDUAL DRUGS IN 183 PREVIOUSLY UNTREATED CASES—ONTARIO, 1960

	Streptomycin		*PAS*		*INH*	
Resistant						
—fully	13	7.1%	5	2.7%	—	—%
—partially	36	19.6%	10	5.4%	2	1.0%
	49	26.7%	15	8.1%	2	1.0%
Susceptible	134	73.3%	168	91.9%	181	99.0%
Total	183	100.0%	183	100.0%	183	100.%

TABLE XVI.—SUSCEPTIBILITY STUDIES ON CULTURES OBTAINED FROM 149 CASES WITH A RECORD OF PREVIOUS TREATMENT—ONTARIO, 1960

	Number	*Percentage of total*
Resistant to three drugs		
—fully to 3	21	14.1
—fully to 1, partially to 2	2	1.3
—partially to 3	1	0.7
Resistant to two drugs		
—fully to 2	7	4.7
—fully to 1, partially to 1	6	4.0
—partially to 2	5	3.4
Resistant to one drug		
—fully	17	11.4
—partially	18	12.1
Fully susceptible to three drugs	72	48.3
	149	100.0

It is likely that the incidence of infection with resistant tubercle bacilli in the community at the present time probably lies somewhere between borders delineated by the findings in these two groups of patients.

TABLE XVII.—SUSCEPTIBILITY STUDIES ON CULTURES OBTAINED FROM 149 CASES WITH A RECORD OF PREVIOUS TREATMENT—ONTARIO, 1960

	Streptomycin		*PAS*		*INH*	
Resistant						
—fully	41	27.5%	28	18.8%	33	22.1%
—partially	28	18.8%	7	4.7%	6	4.0%
	69	46.3%	35	23.5%	39	26.2%
Susceptible	80	53.7%	114	76.5%	110	73.8%
	149	100.0%	149	100.0%	149	100.0%

In Table XVIII a comparison is made between the more important aspects of this problem found in these two groups of patients.

TABLE XVIII.—COMPARISON OF SUSCEPTIBILITY TO STREPTOMYCIN, PAS AND INH OF PATIENTS WITH AND WITHOUT PREVIOUS ANTIBIOTIC TREATMENT—ONTARIO, 1960

	183 patients with no previous treatment	*149 patients with previous treatment*
Full resistance to at least one drug	9.8%	35.5%
Any degree of resistance to at least one drug	27.3%	51.7%

The fact that between one-quarter to one-half of these patients harbour tubercle bacilli with some degree of resistance to at least one drug indicates that great care should be exercised in the actual treatment of patients with antituberculous drugs, lest this proportion increase rapidly in the years to come. While we should remain hopeful that new more powerful drugs will be introduced in the treatment of tuberculosis, it would be folly to allow the effectiveness of the existing drugs to become dissipated by the careless supervision of their use.

SUMMARY AND CONCLUSIONS

During 1960 there were 157 deaths attributed to tuberculosis in Ontario, giving the mortality rate of

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2.6 per 100,000, the lowest ever to be recorded. Of these deaths 61% occurred in people over 60.

Tuberculosis is still a common disease despite its low mortality. A total of 2030 persons developed active tuberculosis in 1960, giving a morbidity rate of 33.3 per 100,000, or one case for each 3000 people. The highest incidence in active tuberculosis is found among men over 45; the older the man the more likely he is to develop active disease.

Types of tuberculosis which develop early after primary infection are becoming uncommon. The incidence of tuberculous meningitis has decreased more than 20 times in the last 40 years. Pulmonary tuberculosis of "reinfection" or "adult" type is the most common form of the disease. Calculating its incidence among the infected, tuberculin-positive population, it is shown that the highest risk of its development occurs among infected adolescents and young adults.

It is estimated that about one-fifth of the active cases of tuberculosis are not admitted to sanatoria; only about one-half of these apparently receive antimicrobial treatment at home. Sanatorium treatment remains the best treatment for tuberculosis, and every effort should be made to have every active case admitted for at least a brief initial period of therapy. "Uncooperative" patients, unwilling or unable to submit to sanatorium treatment, should be either committed or treated with antituberculous agents on an ambulatory basis.

Private physicians, general hospitals and chest clinics are responsible for the diagnosis of some 70% of active cases.

The incidence of active tuberculosis among Indians is at least ten times higher than among the white population. In the foreign-born group tuberculosis is probably almost twice as common as in the Canadian-born population.

Active tuberculosis is not spread evenly throughout the province: Northwestern Ontario showed the highest incidence, 62.0 per 100,000; however, when the Indian population is excluded Northeastern Ontario leads, with the rate of 41.4 per 100,000.

Resistance of tubercle bacilli to the three main drugs used in the treatment of tuberculosis, streptomycin, INH and PAS, is not uncommon. The available data indicate that some degree of resistance to at least one drug is encountered in one-quarter to one-half of the cases. Great care has to be exercised in the treatment of tuberculous persons lest a further rise in the incidence of resistant strains of tubercle bacilli preclude the effective use of antituberculous drugs.

We wish to thank Dr. W. G. Brown, Deputy Minister of Health, for his permission to submit this paper for publication. We are very grateful to Dr. S. A. Holling, Director, Division of Tuberculosis Prevention, for his continuous encouragement, interest and support. We wish to thank many colleagues for their helpful criticisms and suggestions, and the members of the Section of Epidemiology and Research for their diligent and meticulous work.

THE DIFFERENTIAL DIAGNOSIS OF CONGENITAL HEART DISEASE
III. LESIONS WITH RIGHT-TO-LEFT SHUNT*

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THE differential diagnosis of cyanotic congenital heart disease often presents a perplexing problem for which a planned approach is particularly essential. In two previous communications the classification of congenital lesions into those with no shunts, those with left-to-right shunts, and those with right-to-left shunts was emphasized.[2, 3] In each case the group was further subdivided into those with left, right, or combined ventricular hypertrophy. This procedure will be continued in the present discussion.

The first diagnostic step is to establish the presence of cyanosis by an examination of the colour of the skin, nailbeds and mucous membranes, and by a search for clubbing of the digits. The fingers and toes must then be compared to detect differential cyanosis. In borderline cases, particularly where a relative anemia conceals the cyanosis, the clinical suspicion is confirmed by measurement of the arterial oxygen saturation.

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Next, consideration must be given to other possible causes of cyanosis. Poor peripheral blood flow, such as occurs when the extremities are cold, or the low cardiac output of congestive heart failure, myocardial disease, or central obstructive lesions may be to blame. Unsuspected polycythemia from any cause may also lead to confusion. In the neonatal period cyanosis is very common and the subject must be examined for:

1. Pulmonary disease – atelectasis, pneumonia, hyaline membrane disease, diaphragmatic hernia, tracheo-esophageal fistula.
2. Cerebral injury.
3. Shock–sepsis, adrenal hemorrhage, electrolyte deficiency.
4. Congestive heart failure.
5. Rare lesions–tetany, congenital methemoglobinemia.

Elimination of these possibilities is followed by establishment of ventricular hypertrophy – right, left, or combined. In infants the electrocardiogram is the most reliable source of this information, the results of clinical and radiographic examination often being quite difficult to interpret.

The initial evaluation is completed by determination of the state of the pulmonary vascularity, separation of cyanotic patients into those with increased or decreased pulmonary blood flow being of fundamental importance. Here the radiograph is the principal guide, although a rapid respiratory rate suggests pulmonary congestion.

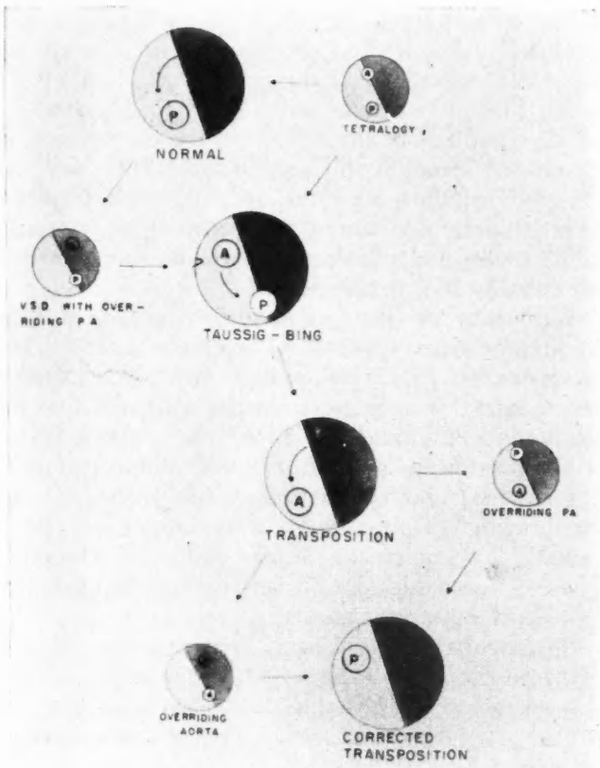

Fig. 1.—Schematic diagram of horizontal cross-sections of the heart to illustrate the effect of varying degrees of rotation of the origin of the great vessels. A = aorta; P = pulmonary artery.

With these two facts, the electrocardiographic evidence of ventricular hypertrophy and the radiographic picture of the pulmonary vasculature, the diagnostic problem becomes much easier. Familiarity with the diagnostic possibilities will reveal that a certain group of three lesions must be considered regardless of whether the patient has right, left, or combined ventricular hypertrophy. This group of the "Big Three" includes truncus arteriosus, transposition of the great vessels, and single ventricle.

A slight digression may be allowed to aid our understanding of the various forms of the transposition complex. Fig. 1 explains them as members of a family that have varying degrees of rotation of the origin of the trunks of the pulmonary artery and the aorta. Transposition signifies that the aorta arises anterior to the pulmonary artery; corrected transposition that the anterior aorta originates from the arterial ("left") ventricle and the posterior pulmonary artery from the venous ("right"). Until this is clearly understood consideration of the anatomical structure of the ventricles and the atrioventricular valves will be confusing.

The combination of cyanosis with a continuous murmur is unusual unless the patient has undergone a Blalock or Potts-Smith operation. The diagnostic possibilities include truncus arteriosus, tetralogy or pulmonary atresia with bronchial collaterals, total anomalous venous return, pulmonary arteriovenous fistula, pulmonary artery–left atrial shunt, and coarctation of the pulmonary arteries with an associated right-to-left shunt.

Left Ventricular Hypertrophy with Right-to-Left Shunt

The conditions that should be considered in the presence of these findings include:

1. Atresia of the right side of the heart: (a) Tricuspid atresia; (b) Pulmonary atresia.
2. Truncus arteriosus.
3. Transposition of the great vessels.
4. Single ventricle with pulmonic stenosis.

Cardiac catheterization and angiocardiography are often needed for definitive separation of these lesions. Patients with lesions in the first three groups are seriously ill and attract attention in the first few days or weeks of life, while an older child with a small heart probably has a single ventricle and pulmonic stenosis. If the lung fields are plethoric and the heart is large, either truncus arteriosus or some form of transposition of the great vessels is present. Diminished pulmonary vascularity and a small heart signify tricuspid atresia, pulmonary atresia, or single ventricle with pulmonic stenosis.

1. ATRESIA OF THE RIGHT SIDE OF THE HEART

(a) *Tricuspid Atresia*

This is the common abnormality in a cyanotic infant with left ventricular hypertrophy. Clinical recognition depends on the presence of "a" waves in the jugular venous pulse along with visible and palpable evidence of left ventricular hypertrophy.[4] Left axis deviation, a horizontal axis, and right atrial hypertrophy in the electrocardiogram clinch the diagnosis. Tricuspid atresia may occur *alone or with transposition* of the great vessels, either type having decreased, normal, or increased pulmonary vascularity. Decreased or normal vascularity and a small heart favour normal great vessel arrangement, however, whereas increased pulmonary blood flow and a large heart usually indicate the presence of transposition. In the latter case, if the pulmonary flow is great enough, cyanosis will be minimal until the heart fails.

(b) *Pulmonary Atresia*

There are two types of pulmonary atresia: 85% of the cases have a small right ventricle, while 15%, which may evolve from the others, have a large right ventricle and electrocardiographic evidence of right ventricular hypertrophy.[1] In those with a small right ventricle there is electrocardiographic evidence of left ventricular hypertrophy, but, unlike tricuspid atresia, the standard limb leads show right axis deviation and a vertical heart.

A continuous murmur from a patent ductus or collateral vessels may be present, but often there is no murmur at all.

Pulmonic stenosis severe enough to cause cyanosis may be confused with complete atresia. The former, however, will show severe right ventricular hypertrophy on the electrocardiogram. Pulsation of the neck veins and liver, marked cardiac enlargement, and a harsh basal systolic ejection murmur may also be found in severe pulmonic stenosis.

2. Truncus Arteriosus

Severe respiratory distress in the neonatal period, failure to gain weight, and intractable congestive failure are commonplace, with cyanosis developing at some stage. Most of the patients die within six months.

A systolic murmur at the base and a loud single second sound are heard. An apical systolic click that does not vary with respiration betrays the high flow in the dilated aorta. When there is associated aortic insufficiency, as frequently occurs, a diastolic blow along the left sternal border strengthens the diagnosis.[4]

The radiograph shows increased pulmonary vascularity, and sometimes suggests a high origin of the pulmonary arteries from the ascending aorta. A retrograde aortogram will confirm this impression.

It is useful to remember that a ventricular septal defect is present in 100% of the cases, amounting to a single ventricle in 25%, and that a right aortic arch occurs in 60%.

3. Transposition

When transposition is accompanied by a ventricular septal defect and high pulmonary blood flow, left ventricular hypertrophy is usually found. The axis may be either right or left. This lesion is suspected when the combination of a large heart and pulmonary plethora occurs. Differentiation from tricuspid atresia with transposition requires angiocardiography or catheterization.

4. Single Ventricle with Pulmonic Stenosis

The presence of pulmonic stenosis increases the degree of cyanosis but protects the lungs from excessive blood flow and the heart from congestive failure; consequently, the patient may live for some time with surprisingly few symptoms. An angiocardiogram must be performed to differentiate this condition from tricuspid atresia.

Right Ventricular Hypertrophy with Right-to-Left Shunt

These abnormalities comprise the largest group of cyanotic conditions, and hence a few generalizations will be useful. The diagnosis is simplified if the lesions are separated according to the incidence of congestive failure, the state of pulmonary vascularity, and the heart size.

The occurrence of *congestive heart failure* in the neonatal period signifies a serious and usually fatal lesion such as left-sided atresia involving the aortic or mitral valve or the pulmonary veins. The age of onset of symptoms and the gravity of the situation make these conditions comparable to the atresias of the right side of the heart, but the electrocardiogram will separate the two groups. The onset of congestive failure after the neonatal period makes isolated pulmonic stenosis most likely if the pulmonary vascularity is decreased, while transposition is probable if it is increased.

The state of the *pulmonary vasculature* can frequently be suspected clinically: cyanotic conditions with high pulmonary flow are usually accompanied by dyspnea. In the absence of congestive failure a *small heart* with anemic lung fields is likely tetralogy of Fallot, while plethoric lungs signify total anomalous venous return below the diaphragm. A *large heart* with diminished pulmonary flow occurs in severe pulmonic stenosis, whereas increased pulmonary vascularity usually represents a transposition.

Once again the "Big Three" will be present somewhere in the classification. The list includes:

1. Atresia of the left side of the heart, (a) Aortic atresia; (b) Mitral atresia; (c) Total anomalous pulmonary venous drainage.
2. Lesions with decreased pulmonary vascularity, (a) Pulmonic atresia, (i) with large right ventricle, (ii) with ventricular septal defect; (b) Pulmonic stenosis, (i) alone, (ii) with ventricular septal defect (tetralogy of Fallot), (iii) with single ventricle (large ventricular septal defect), (iv) with transposition; (c) Ebstein's anomaly.
3. Lesions with increased pulmonary vascularity, (a) Transposition; (b) Truncus arteriosus; (c) Single ventricle; (d) Taussig-Bing deformity; (e) Secondary pulmonary hypertension.

1. Atresia of the Left Side of the Heart

(a) *Aortic and Mitral Atresia*

Cardiac enlargement, cyanosis, increased pulmonary vascularity, congestive heart failure, and right ventricular hypertrophy are found in the neonatal period with either lesion. Aortic atresia with a hypoplastic arch and a small left ventricle may occur alone, but is often associated with mitral stenosis or atresia, a large pulmonary artery, and a patent ductus. In either case the outlook is grave, and surgical relief is unlikely. The hypertrophied right ventricle may be palpated, but the most important clue, if it is present, is an early *systolic click* originating from the dilated pulmonary artery. This pulmonary click is unusual, however, because it is heard at the apex, which is formed by the right ventricle, and it does not vary with respiration.[4]

The radiograph may show the honeycomb appearance of pulmonary venous congestion. Angiocardiography will clarify the diagnosis.

Infantile coarctation of the aorta with a patent ductus resembles these conditions, but the signs of

right ventricular failure predominate and rarely differential cyanosis may be noted, the toes being more cyanotic than the fingers.

(b) *Total Anomalous Pulmonary Venous Drainage*

Severe dyspnea and an ashen-grey colour attract attention to the newborn infant. A triple rhythm is very frequent and a continuous murmur may be present. An *atrial scratch* caused by the dilated tense right atrium may be heard: it may be systolic, diastolic, or both; it appears to be superficially located; and its intensity is affected by changes in the pressure of the stethoscope on the chest wall. A similar scratch may be heard whenever the right atrium is tense and dilated, such as in Ebstein's anomaly or in a large atrial septal defect.[4]

The chest radiograph demonstrates pulmonary congestion often with a characteristic *ground glass appearance* to the lung fields. If the pulmonary veins drain below the diaphragm, a large liver may be found combined with a heart that is surprisingly small in the face of so much pulmonary congestion. Cyanosis and pulmonary congestion are marked in these cases as well as in those where the drainage into the caval system above the diaphragm is stenosed. When the pulmonary return is unimpeded, the pulmonary blood flow is huge, the cyanosis is less marked, and the heart is greatly enlarged.

The electrocardiogram reveals marked right ventricular hypertrophy with a qR pattern in V_1 and an inverted T wave extending for a variable distance across the precordium.

Cardiac catheterization will show a marked step-up of oxygen saturation at the site of entrance of the pulmonary venous drainage.

2. LESIONS WITH DECREASED PULMONARY VASCULARITY

(a) *Pulmonary Atresia*

(i) *With a large right ventricle.* The original left ventricular hypertrophy and right axis deviation of the type with a small right ventricle change to right ventricular hypertrophy and right axis deviation as the ventricle enlarges. Absence of the main pulmonary artery and a bronchial pattern to the pulmonary vasculature on the radiograph are suggestive, but an angiocardiogram is required to confirm the diagnosis.

Most of the patients die in a few months unless surgical intervention is possible.

(ii) *With ventricular septal defect*—This lesion is also called pseudotruncus, and may be considered to be a severe form of tetralogy. The chest radiograph is the same as in pulmonary atresia, but the infants are often not so ill. They fail to grow normally and are deeply cyanosed, but, as is the case in tetralogy, congestive failure is not common. An angiocardiogram is required.

(b) *Pulmonic Stenosis*

(i) *Alone.*—Severe pulmonic stenosis rather than pulmonary atresia is suggested by a moon face, "a" waves in the jugular pulse, hepatomegaly, a harsh stenotic murmur and thrill at the base, a second sound that is diminished in intensity or absent at the base, severe right ventricular hypertrophy and right atrial hypertrophy on electrocardiogram, and a large heart on the radiograph. In other words, signs of marked right ventricular work and back pressure are noted.

It is often possible by phonocardiography to record the delayed weak pulmonic closure in isolated pulmonic stenosis, whereas in tetralogy this is rare.

(ii) *With ventricular septal defect* (tetralogy of Fallot).—A history of squatting, a small heart, a loud single second sound, and only moderate right ventricular hypertrophy on the electrocardiogram are characteristic.

The radiograph shows a small heart with diminished pulmonary vascularity. A right aortic arch is common: this finding and the small heart would almost exclude a diagnosis of transposition.

The history may differentiate tetralogy from transposition with pulmonic stenosis. Anoxic spells are more common in tetralogy, and a delayed onset of cyanosis until several weeks or months after birth sometimes occurs with tetralogy, but never with transposition. An episode of congestive failure rules out tetralogy.

Tetralogy is distinguished from severe pulmonic stenosis by several features. A history of squatting and a right aortic arch are very rare in isolated pulmonic stenosis, while both are common in tetralogy. The second sound at the base is diminished or absent in severe pulmonic stenosis. Finally, electrocardiographic evidence of advanced right ventricular and right atrial hypertrophy is rare in tetralogy because decompression of the right ventricle can occur through the ventricular septal defect. It is helpful to compare the findings in tetralogy and pulmonic stenosis as follows:

Pulmonic Stenosis

(i) Mild: Soft murmur, delayed soft pulmonic closure, mild right ventricular hypertrophy, no cyanosis.

(ii) Severe: Harsh prolonged murmur, absent second sound at the base, severe right ventricular hypertrophy, cyanosis present.

Tetralogy

(i) Mild: Moderate murmur, single second sound, moderate right ventricular hypertrophy, mild or absent cyanosis.

(ii) Severe: Faint murmur, single second sound, moderate right ventricular hypertrophy, cyanosis present.

The increased flow across the pulmonic valve in the milder and less cyanotic forms of tetralogy is indicated by the longer and louder systolic murmur and at times by a faintly audible pulmonic closure.[5]

(iii) *With single ventricle* (large ventricular septal defect) – Single ventricle with pulmonic stenosis may mimic tetralogy. Enlargement of the right atrium on radiograph and P pulmonale on the electrocardiogram suggest the presence of single ventricle. Other electrocardiographic findings of single ventricle are discussed later. Angiocardiography or cardiac catheterization is required to establish the diagnosis.

(iv) *With transposition*—The abnormal origin of the pulmonary artery and its associated stenosis may be suspected if the second heart sound is maximal at the second right interspace and a diamond-shaped systolic murmur is heard in the same area.[4] Aortic stenosis, which could cause the same murmur, does not produce cyanosis.

The radiographic diagnosis is based on identification of the two primary features—diminished pulmonary blood flow and abnormal origin of the great vessels. On a plain chest radiograph the aorta may be noted to ascend on the left cardiac border and to give a convexity to this region with a downturned apex. Angiocardiography will confirm the anterior position of the aorta and may show the pulmonic stenosis. Cardiac catheterization demonstrates the characteristic feature of transposition, that is, pulmonary arterial oxygen saturations that are consistently above those in the aorta; it will also reveal the pulmonic stenosis and the anterior aorta.

(c) *Ebstein's Anomaly*

Auscultation may reveal a closely split second sound with a diminished pulmonic component (the right-to-left shunt and the tricuspid regurgitation both shorten the right ventricular ejection time); a systolic-diastolic atrial scratch (dilated tense right atrium); a loud atrial sound (fourth heart sound) maximum at the second left interspace and along the right sternal border; an opening snap maximum over the lower sternum (fibrosed tricuspid valve); a systolic murmur at the lower left sternal border (tricuspid regurgitation); and a diastolic rumble in the same location (rigid deformed tricuspid valve). Thus, the tense enlarged right atrium accounts for two unusual auscultatory findings and the deformed tricuspid valve for three more. Classical cases will show several of these features, while mild ones may have none of them.

Cardiac enlargement and decreased pulmonary vascularity are present on the radiograph. The distinguishing feature is the unique electrocardiographic pattern that includes right bundle branch block, low voltage over the right chest, P waves that are frequently tall and prolonged, and a multiphasic and prolonged QRS.

3. LESIONS WITH INCREASED PULMONARY VASCULARITY

(a) *Transposition*

A rapidly enlarging, egg-shaped heart, with a narrow vascular pedicle, increased pulmonary vascularity, cyanosis, and a history of congestive failure in early infancy—these findings are typical of transposition. About one-third of the cases have right ventricular hypertrophy and right axis deviation.

If an early systolic click is heard at the apex, signifying high flow through the vessel arising from the left ventricle, and if the intensity of the click varies with respiration, thus identifying the vessel as the pulmonary artery, the diagnosis of transposition with high pulmonary flow can be made.[4] However, it cannot be distinguished clinically from the Taussig-Bing deformity, which is functionally a close relative.

Reliance is placed on radiographic techniques to prove the diagnosis of abnormal origin of the great vessels. Cardiac catheterization will demonstrate the greater oxygen saturation in the pulmonary as compared to the peripheral arterial blood.

(b) *Truncus Arteriosus*

This lesion may show right ventricular hypertrophy on the electrocardiogram. The clinical and radiographic pictures are as previously described.

(c) *Single Ventricle*

In the absence of either pulmonic stenosis or high pulmonary vascular resistance, the pulmonary blood flow can be enormous. Although this results in minimal cyanosis, severe dyspnea is present and congestive failure develops early. This is the picture in 75% of the patients with single ventricle. Also associated with single ventricle are transposition in about 75% (10% of transpositions have a single ventricle), atrial septal defect in 75%, and a rudimentary outlet chamber in 75%.[1]

Any of the following electrocardiographic patterns should arouse suspicion of a single ventricle:

1. Equiphasic complexes across the precordium.
2. Negative complexes across the precordium.
3. A qR pattern over the right precordium in a patient with transposition.

Cardiac catheterization and angiocardiography are required to establish the diagnosis.

(d) *Taussig-Bing Deformity*

This lesion, like transposition with high pulmonary flow, may be identified by the detection of an apical early systolic click that varies with respiration. Cyanosis is present from birth. The angiocardiogram shows simultaneous filling from the right ventricle of a small posterior aorta and a large anterior pulmonary artery.

(e) *Secondary Pulmonary Hypertension*

Late in the course of any large left-to-right shunt, severe pulmonary hypertension may develop and lead to cyanosis. If a ventricular septal defect is the primary lesion, the complex is referred to as Eisenmenger's syndrome.

The late onset of cyanosis is an important diagnostic clue. The second heart sound at the base is increased in intensity and may be palpable. Its character depends on the primary lesion.[6] Angiocardiographic filling of only an anteriorly placed pulmonary artery from the right ventricle favours Eisenmenger's syndrome as opposed to Taussig-Bing deformity, in which the aorta and the pulmonary artery are filled simultaneously, and transposition, in which both are filled simultaneously but the aorta is anterior.

To review, congestive failure in the neonatal period is caused by left-sided atresia or total anomalous pulmonary venous drainage. Such patients rarely survive more than a few months. In an older child with a large heart the onset of congestive failure favours the diagnosis of transposition when the pulmonary flow is increased, and severe pulmonic stenosis when it is decreased. A cyanotic child with a small heart and no history of failure probably has tetralogy of Fallot.

Emphasis must also be placed on the necessity of keeping the "Big Three" of truncus arteriosus, transposition of the great vessels, and single ventricle constantly in mind during the examination of a cyanotic child.

Combined Ventricular Hypertrophy with Right-to-Left Shunt

Only electrocardiographic evidence of involvement of both ventricles separates this group from the previous two. All the lesions have been discussed already and the list includes, of course, the "Big Three". They are:

1. Transposition
2. Truncus
3. Single ventricle
4. Secondary pulmonary hypertension.

No further description of these is needed.

SUMMARY

Patients suspected of having a *right-to-left shunt* should be examined first for another cause of cyanosis. In all of the right-to-left shunts, regardless of the type of ventricular hypertrophy, the trio of transposition, truncus, and single ventricle enters the diagnostic arena.

1. *Left ventricular hypertrophy* connotes atresia of the right side of the heart, truncus arteriosus, transposition, or singie ventricle with pulmonic stenosis.

The first three lesions cause symptoms early in infancy. The electrocardiogram in tricuspid atresia shows left ventricular hypertrophy, left axis deviation, and a horizontal heart; and a complicating transposition is suspected if the radiograph reveals a large heart and increased pulmonary vascularity. The electrocardiogram in pulmonary atresia with a small right ventricle also shows left ventricular hypertrophy, but with right axis deviation and a vertical heart. A truncus is recognized by the severe respiratory distress, characteristic auscultatory findings, high origin of the pulmonary arteries on the radiograph, and death by six months of age. Single ventricle requires special studies for diagnosis.

2. *Right ventricular hypertrophy* occurs in lesions with neonatal congestive failure, with decreased pulmonary vascularity, and with increased pulmonary vascularity.

(a) *Neonatal Congestive Failure*

These serious lesions include aortic and mitral atresia and total anomalous pulmonary venous drainage. Severe cyanosis and congestive failure and early demise are characteristic. A systolic click at the apex is heard with aortic or mitral atresia. Anomalous pulmonary drainage often produces on the radiograph a ground glass appearance to the lung fields while an atrial scratch and a continuous murmur may be heard. Catheterization and angiography are required in this group.

(b) *Decreased Pulmonary Vascularity*

Pulmonary atresia is suspected by the bronchial pattern of the pulmonary vasculature, and angiography is confirmatory; severe pulmonic stenosis has a characteristic murmur and second heart sound, and marked right ventricular hypertrophy on the electrocardiogram; tetralogy has a history of squatting, a small heart, absence of congestive failure, and moderate right ventricular hypertrophy; and transposition shows an enlarging heart, and a tendency to congestive failure, but requires for its diagnosis cardiac catheterization and angiographic demonstration of an anterior aorta. Ebstein's anomaly has a specific electrocardiographic picture, and unusual auscultatory findings related to the large right atrium and deformed tricuspid valve.

(c) *Increased Pulmonary Vascularity*

Truncus arteriosus, single ventricle, and secondary pulmonary hypertension are diagnosed as above; transposition and the Taussig-Bing deformity by an apical systolic click and angiography.

3. *Combined ventricular hypertrophy* signifies the presence of transposition, truncus arteriosus, single ventricle, or pulmonary hypertension secondary to a previously existing left-to-right shunt.

The author wishes once again to express his indebtedness to Dr. Benjamin Gasul, Cook County Hospital, Chicago; to Dr. Alexander Nadas, The Children's Hospital, Boston; and especially to Dr. Kareem Minhas, Illinois Research and Educational Hospitals, Chicago.

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MEN AND BOOKS

THE WISEST MAN IN ICELAND

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MANY OF those who enjoy the smooth grey novels of Sir Charles Snow dealing with administrative, academic, scientific, and political life in England, realize that they are addicted. One can never be quite sure that one's best friends, those whom one has known since medical school, will have a palate for such a dry and delicately flavoured wine. As likely as not they will show the cloven hoof and pronounce it flat and corked. They will find the monochromatic prose dull and the intricate dissection of the small worlds, which Sir Charles portrays so well and knowledgeably, boring. Yet I find it hugely fascinating to read about the strivings of shrewd, tough, intelligent and ambitious men in a setting where a word over the port or a nod after the brandy can make or break a career. In marked contrast to the world of the Snow men who struggle in private and almost always behind the scenes to obtain advancement and wield authority are the astonishingly public politics of the United States portrayed in Allan Drury's "Advise and Consent".[1] The style and setting of these two writers offset each other splendidly. Where Snow is grey, Drury is purple. Where Snow ambles, Drury stampedes. Yet both writers give one an admirable feeling for a particular aspect of life in their very different countries.

Few of us can ignore governments today. We may wish it were otherwise, but we know in our hearts that government and medicine must confront each other frequently in the years ahead. We have a duty to be curious and well informed about the way in which politicians approach those technical and scientific matters which are our business, and the way in which they deal with their own affairs. Politicians, like the well-informed Enoch Powell,[2] the British Minister of Health, are fully aware that we and they are likely to be on opposite sides of the fence. Perhaps there is no way to develop a taste for the Snow novels, or for that matter the much juicier writing of Drury, but if there is a way of getting into the world of the Snow men by easy stages, then the Godkin Lectures[3] on "Science and Government" which Sir Charles gave at Harvard last year must be it. There may be others who know more about the way in which science impinges on the governing of men and about the impingement of government on science. There are certainly those who write less pedestrianly, but few can rival him for clarity, vividness, and brevity. These are memorable lectures.

While Drury's "Advise and Consent" gives a massive, though often disconcerting and long-winded picture of the weakness and strength of public American government, in "Science and Government" Sir Charles forsakes fiction. He tells of the strange affair culminating in that bitter struggle between Sir Henry Tizard and Professor F. A. Lindemann (Lord Cherwell).

The Godkin Lectures are only 90 pages of large type, so the busiest man has no excuse for not reading them. The story which Sir Charles has to tell is so bizarre that if it had not been attested to by others involved, such as Professor Blackett, one would have to conclude that he had chosen a more sensational and less truthful theme for his novels than is his wont. Professor Lindemann seems to have been one of those unlikely men whom the wise fiction writer avoids simply because they are not quite credible. There is surely a certain improbability about a first-class scientist who preferred parachute mines to radar as a way of stopping even the very slow bombers of the 1930's. But when such a professor becomes the chief scientific adviser to Sir Winston Churchill at the height of a desperate war in which the device he opposed so bitterly played a decisive part, the regular reader of fiction finds this altogether too much. And then Lindemann ousts from high public office Sir Henry Tizard who had backed radar against his parachute mine. Of course it was all done with true British decorum. Indeed, both Tizard and Lindemann were fellow members of the Athenæum Club until their deaths.

Once installed as Britain's chief scientist, and having rid himself of Tizard, Lindemann became the diligent advocate of massive aerial bombing in Germany. This was a rather dubious military bargain which involved exchanging two British or American aircrew for every five German civilians killed. There is now much evidence that this bombing had far less effect upon German industry than was supposed at the time. Snow notes that these matters were fought out in private, so that hardly anyone outside of a very small circle had any idea what was happening.

It is easy to be reassured with a comfortable thought that that was war, and we are now at peace: that it could not happen here or now. But couldn't it? Doesn't it?

What lessons does Sir Charles have for us in medicine apart from those which we may learn as citizens? I think we can learn a good deal about governments from him. He writes, "We can collect quite a few working tips from the Tizard-Lindemann story. For instance the prime importance in any crisis of action of being positive what you want to do and of being able to explain it. It is not so relevant whether you are right or wrong.

That is a second order effect. But it is cardinal that you should be positive . . . . Even at the highest level of decision men do not relish the complexity of brute reality and they will hare after a simple concept whenever one shows its head." This is surely something to ponder about.

He continues, "Remember, administrators are by temperament active men. Their tendency, which is strengthened by the nature of their job, is to live in the short term, to become masters of the short term solution."

The trouble is that the simple short-term solution is often no more than palliative. Those who advocate more complicated courses of action often do not trouble to put their ideas in some form which administrators, whether political or professional, can understand. Perhaps they feel that theirs is too serious a matter for catch words or slogans. But unless we realize that administrators place great value on what seems to be simple, positive, and easily explained, we shall not learn from our past mistakes. Then we shall deserve to be ranked with those to whom Sir Charles applies a formidable and nagging phrase from the Icelandic sagas: "Snorri was the wisest man in Iceland who had not the gift of foresight."

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VIEWPOINTS

SOME GUIDING PRINCIPLES IN THE EDUCATION OF PHYSICAL AND OCCUPATIONAL THERAPISTS*

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GREAT interest has recently been aroused over the education of physical and occupational therapists. This has been due to world-wide shortages of these valuable individuals in the treatment of the sick and disabled. Many ideas for improvement of our training methods have been suggested by interested parties. While some of these merit careful consideration, many of them have been offered from only one point of view. This paper will attempt to deal with the problem as a whole. Unless the viewpoints of the teacher, the students, the patients, the universities, the hospitals and the doctors are carefully examined, many problems pertinent to the shortage of therapists can be easily overlooked and a temporary solution reached that only creates further problems. The predominant reason for the present-day concern with the education of the physical and occupational therapist is that the demand exceeds the supply. While this is true all over the world, the condition is most acute in North America, where physical treatment developed later than in Europe. The whole problem requires long-term remedies, some of which I hope to discuss in this paper.

THE IMPORTANCE OF AFFILIATION

The affiliation of the training school is the first and most important consideration. Should it be attached to a hospital only or to both a hospital and a university? To understand why this question arises at all it is necessary to realize that in England a special educational condition exists. There, the older medical schools are part of a hospital and have had no university affiliations until recently. These hospital medical schools have complete medical faculties with extensive laboratories of their own. Therefore, the hospitals have at hand medical teaching facilities which are available to any other training school that they may establish. Hospital schools of physical and occupational therapy have made use of these teaching establishments for the training of their students. Here in Canada, and indeed throughout North America, no similar hospital medical schools exist; the faculties of medicine are all attached to universities. No hospital in itself has any available facilities for teaching subjects such as physics, anatomy or physiology, except in a very meagre way to the nurses. To establish such facilities in a hospital would be prohibitively expensive, and in most cases not suited to our needs. A hospital course would not be recognized by the universities, and as a result the physiotherapy graduate of such a course would be unable to take advantage of postgraduate university courses, since these are as a rule only open to university graduates.

THE PRACTICAL OR "APPLIED" COURSE

In addition to this, simple hospital courses of the practical or applied type are insufficient for

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a physical or occupational therapist. She requires a well-rounded education of the type available in a university. It is important that she have the basic training for dealing with all types of people. She must be able to instruct the patient and guide him, besides understanding the complicated procedures the physician is undertaking. To deal with such situations a university grounding is essential. Medical and surgical practice are continually changing, so that it is best to have a basically trained individual who can adapt to these changes. A practical or applied course produces an individual with a built-in obsolescence. This is harmful to the patient and very frustrating to the physiotherapist or occupational therapist, for as time passes she finds herself inadequate to deal with the problems that arise. I feel, therefore, that a school of physical and occupational therapy must be attached to a university.

THE CURRICULUM: PHYSICAL AND OCCUPATIONAL THERAPY

Having made this decision, the next problem requiring consideration is the subjects to be studied in such a course. It is important that proper university standards be adhered to both in admissions and throughout the course. If double standards are permitted either in the admission requirements or in the type of course set up, then such a course at once becomes a haven for the academic rejects from other courses, who should never be at the university at all. Next the problem of separation of the physical therapists from occupational therapists must be considered. I feel that a definite division has to be made here. The subjects suited to a physical therapist are not the same as those suited to an occupational therapist. Their temperaments are different. The training of the physical therapist should be the B.Sc. type, as these students tend to be scientifically minded. That of the occupational therapist will be of the B.A. or liberal arts type. In spite of attempts that have been made in three Canadian schools, none has really succeeded in fusing these two types of therapist into one. Although quite a number have graduated with the combined training, all but a small handful practise either one or the other profession. Indeed, in Montreal there is really only one combined graduate who works in both spheres and this to a very limited extent. I find that students in physical therapy have no interest in occupational therapy training and vice versa. Students will often try, if at all possible, to arrange their work to avoid the subject they are not interested in. The students who come to the school, arrive with a predetermined idea that they want to do either physical or occupational therapy, and none, or very few of them, ever transfer.

For admission to a school of physical therapy the matriculant should present the standard B.Sc. subjects of mathematics, physics and chemistry, in addition to two other subjects which need not be scientific. Using the college boards scores, the requirements would be scholastic aptitude tests in two parts, verbal and mathematical, and three achievement tests, a total of 2500-3000 marks being required with 500 as a base in each subject. The standing must be that of any other student entering the B.Sc. course; that is, nothing below the minimum of the university entrance. Once the student has been admitted, her studies must include satisfactory science credits with suitable scientific continuation subjects. All courses should be regular departmental courses provided for the ordinary B.Sc. students. These will be courses standardized by the departments concerned at a reasonable intellectual level. Special spoonfed courses are to be avoided. The subjects will be mathematics, physics, chemistry, biology, English, anatomy, physiology, psychology, sociology, and basic medical concepts with suitable technical training in physical therapy. Such a course provides a good scientific background with adequate professional training.

A parallel course must be organized for the occupational therapists. In my experience a liberal-arts type of course with some science is more desirable for these students. People who are interested in this facet of the healing art are, on the whole, not scientifically minded. Persons of this temperament find the scientific viewpoint narrow and confining. These individuals deal with the patient in relation to the community and they attempt to put him back into his old environment or a new one. Therefore, occupational therapists require a fairly wide knowledge of the essential structure of our culture together with the fundamentals that hold it together. They are more appreciative of the arts subjects both from an academic and a practical point of view. Applicants for this course would present languages, history, mathematics and one other science of a standard similar to that required by the Faculty of Arts. The subjects of their course would be mathematics, biology, anatomy, psychology, history, economics, sociology and languages, with basic medical concepts and suitable technical training in occupational therapy.

THE CANDIDATE

The physical or occupational therapist leads a rather strenuous life; thus, handicapped or diseased personnel are on the whole unable to cope with the work. In some institutions blind people have been trained as therapists. Such blind therapists require special equipment and the aid of a normally sighted person to assist them. Even if the patient will accept treatment from such a handicapped individual, this type of therapist has a limited use. The reaction of the patient to such a handicapped worker can in itself be a stumbling block of considerable dimensions. The man in the

street still reacts unfavourably to the idea of the blind leading the blind. Some deaf and partially crippled individuals have succeeded in graduating, but always in spite of their handicap which they were able to overcome.

DURATION OF THE COURSE

The length of the course is a matter of great importance because when you are dealing with young women there is always the factor of marriage to be considered. Many of the young ladies practise their profession only for a few short years before leaving to organize a home of their own. A long course also defeats its purpose, as the financial rewards are not adequate for the length of time required to complete the training. Therefore, I feel that the course should be organized to satisfy the needs for trained personnel first, and secondly to provide a pool of educated physical and occupational therapists capable of working in the administrative and teaching positions of the larger centres. This can best be done by arranging the academic and technical courses so that a student may graduate with a diploma at the end of three years from junior matriculation or college boards entrance examinations. A holder of such a diploma would satisfy the licensing bodies with her technical training while at the same time having a sound academic foundation. By continuing two more years this diplomate would be able to obtain a degree. The division of the course in this manner provides a group of therapists who are available for work three years after graduating from high school, in addition to those who choose further academic instruction in order to obtain a degree before working. It also enables the student with slender financial resources to augment them by working a year or two and then return to the university to complete the course for a degree.

A DEGREE COURSE FOR THERAPISTS

The degree course establishes the graduate in a position where she is able to undertake further university work such as research when opportunities offer, as they frequently do in larger centres. It also fits the teacher into the pattern of university life. She may start as a demonstrator with a B.Sc. degree and progress to higher degrees, with an increase in her teaching duties. This is far more suitable than the teacher schemes of the associations which really consist in essence of a little practice-teaching with a repetition of the courses already given to the undergraduate.

Research possibilities are extensive. They may be problems related to the basic sciences such as physics and anatomy, or in the practical side of patient treatment. There is no reason why such projects cannot be undertaken by physiotherapists either alone or in conjunction with physicists, anatomists, sociologists, physiatrists, or any other faculty member.

MEN AS THERAPISTS

The training of men is a matter I have considered for some time. Rarely, if ever, does an application arrive from a man with adequate entrance requirements. The number of available positions for men is limited. Most men find the practice somewhat confining and frequently will not abide by the regulations governing their professional confrères. Thus they feel that they should be physicians, but, having an inadequate training for this, they tend to suffer from frustration and frequently set themselves up as unlicensed medical practitioners.

THE ROLE OF THE ASSOCIATIONS

Most of the physical therapists and occupational therapists are members of their respective national associations. These associations, in the author's opinion, sometimes seem to act as pressure groups on both the employer and the universities. This has both good and bad aspects. The good point is that there is an extra academic body interested in training with a certain insistence on the maintenance of minimum standards. The weakness is that, like most associations, they try to raise the standards to an impossibly high level, all the time bemoaning the lack of graduates that this induces. Petty insistence on standardizing the hours and content of the courses is not supported by the universities, who wish to feel free to improve the training and vary their courses from time to time as needs change. Since patients and our governments have only a limited amount of available money for treatment, the association must be careful not to educate its members out of a job by lengthening the training unreasonably. This can happen far more easily than is now realized, since graduates of long courses expect high pay. The energies of the associations would be better spent in fostering research projects.

CONCLUSION

At the present time it would appear that shortages of trained physiotherapists still exist in Canada. This deficiency in our training program is being filled by emigration of surplus physiotherapists from other countries, more especially Europe. We can increase the number of our graduates in three ways: by enlarging present schools, by providing more financial assistance to the students, and by increasing the number of available schools. All these methods should be employed to the full to provide greater numbers of Canadian-trained physiotherapists.

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CASE REPORTS

SYNDROME DE BUDD-CHIARI, SANS ATTEINTE DES VEINES SUS-HEPATIQUES PRINCIPALES ET SANS HYPERTENSION PORTALE

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HISTORIQUE: L'occlusion des veines sus-hépatiques a été décrite pour la première fois en 1846 par G. Budd dans son traité "Diseases of the liver". Lambron aurait cependant rapporté le premier cas en 1842. En 1899, H. Chiari (Prague) en fit une description plus détaillée à l'occasion de trois cas découverts à l'autopsie. Il établit les relations cliniques et pathologiques du syndrome et en précisa les circonstances d'apparition. C'est lui qui donna la définition d'endophlébite oblitérante primitive des veines sus-hépatiques", au syndrome appelé depuis Budd-Chiari. En 1959, Parker[21] a analysé 164 cas, dont très peu ont pu être diagnostiqués ante-mortem. La relative rareté du syndrome peut être due au fait qu'on ne dissèque pas assez attentivement les veines sus-hépatiques à l'autopsie, malgré que Halloch, Watson et Berman de l'Université du Minnesota n'en aient pas trouvé un cas sur 34,000 autopsies. Armstrong et Carnes en citent cinq cas sur 11,979 autopsies.

Histoire du cas:

Il s'agit d'une patiente de 39 ans admise à l'hôpital le 20 septembre 1960, qui, depuis une semaine environ, se plaint de flatulence, de dyspepsie, de nausées sans vomissement, d'anorexie, de douleur à la région épigastrique et à l'hypocondre droit. Elle avait remarqué depuis trois mois que son abdomen se gonflait et devenait douloureux au moment des menstruations. Les menstruations terminées, l'abdomen diminuait de volume. Cependant, depuis les dernières menstruations le 5 septembre 1960, son ventre est resté gonflé et a continué d'augmenter.

Dans les antécédents on note qu'en 1944 elle aurait fait une crise douloureuse étiquetée collique hépatique. Depuis ce temps, elle accusait de la dyspepsie à l'ingestion de graisses. La malade a eu sept grossesses normales suivies d'une môle hydatiforme sans complication.

Examen physique:

La patiente est maigre et légèrement dyspnéique. Les jugulaires ne sont pas dilatées. Les poumons et le cœur sont normaux. La tension artérielle est à 110/70 mm. Hg et le pouls à 76 par minute. On ne note aucune circulation veineuse collatérale abdominale ou thoracique. On remarque cependant une petite hernie ombilicale et une ascite abondante. Le foie n'est pas palpable. Il n'y a pas de splénomégalie. Il n'existe aucun ictère ou œdème des membres inférieurs.

Les résultats des examens de laboratoire se lisent comme suit: l'analyse d'urine est normale; la formule sanguine du 21 septembre 1960 montre une hémoglobine à 106% (15.4 g.), une numération globulaire rouge à 5,700,000/mm.,^{3} une valeur globulaire à 0.95 et une différentielle normale. L'hémogramme pratiqué le 1 octobre donne les valeurs suivantes: hémoglobine 120% (17.1 g.), série rouge 6,700,000/mm.,^{3} série blanche 15,600/mm.^{3} A la répétition des mêmes déterminations le 19 octobre on rapporte: Hg 104% (15 g.), GR 6,200,000, GB 11,550 et plaquettes 230,000/mm.^{3} L'hématocrite se chiffre à 65%.

L'exploration de la fonction hépatique révèle un temps de prothrombine de 16.5 sec. (68%) le 24 septembre et de 15.5 sec (80%) le 8 octobre, un cholestérol à 134 mg. %, un indice biliaire de 7.5 unités, un thymol de 1.0 unité, un Kunkel de 8.5 unités et une céphaline-cholestérol de +++. La glycémie est à 0.93 g. %. La rétention de brome-sulfone-phtaléine à 30 minutes est de 37.2 mg. % (la normale est de 0 à 5 mg. %) et la bilirubine, directe s'élève à 0.85 mg. %, l'indirecte à 0.50 mg. % donnant un total de 1.35 mg. %. L'évaluation des transaminases montre une S.G.O.T. de 80 unités et une S.G.P.T. de 52.

L'électrophorèse des protéines accuse une légère augmentation des globulines β (15%) et des globulines γ (25%) et une légère diminution de la fraction albumine; les valeurs globales sont: albumines 3.15 g. %, globulines 3.38 g. % (a/g 0.93) et protéines totales 6.50 g. %.

Radiographies:

La cholécystographie, le lavement baryté et le transit digestif se sont révélés normaux. Aucune varice œsophagienne n'est démontrée.

Une radiographie simple de l'abdomen montre la présence d'ascite. A la radiographie pulmonaire on note une légère surélévation des deux hémi-diaphragmes, des bandes de condensation aux deux bases, peut-être en rapport avec des zones d'atélectasie et le blocage des deux sinus costo-diaphragmatiques par réaction pleurale récente ou ancienne.

Examens du liquide d'ascite:

Le liquide d'ascite est jaune citrin trouble et visqueux. Le Rivalta est de ++ et l'examen cytologique révèle la présence de neutrophiles (20%), et de lymphocytes (80%); on aperçoit aussi quelques cellules épithéliales et quelques globules rouges.

Trois recherches de cellules néoplasiques se sont montrées négatives. La recherche directe du B.K. et la culture sur Loewenstein ont été aussi négatives.

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Evolution de la maladie:

Devant la présence inexplicable d'ascite, une laparotomie exploratrice a été décidée pour éliminer un adéno-carcinome de l'ovaire ou un fibrome utérin qui réaliserait le syndrome de Meigs. A l'intervention le 29 septembre 1960, on a retiré 4000 cc d'ascite jaune citrin. Les ovaires, l'utérus, la rate, le pancréas, la veine porte, la veine splénique et les reins sont normaux. Le foie semble normal lui aussi. Une biopsie du grand épiploon est practiquée et elle revient normale. Les suites opératoires sont sans particularité.

Mais l'ascite se reforme rapidement et rend la patiente très dyspnéique. Après une ponction le 7 octobre 1960, soit 17 jours après son entrée, on palpe un foie lisse, ferme et très douloureux, dépassant le gril costal d'un travers de main. La rate ne semble pas augmentée de volume. De nouvelles ponctions sont nécessaires à tous les quatre ou cinq jours pour soulager la patiente. La douleur est marquée à l'hypocondre droit et irradie dans l'épaule droite.

Devant ce tableau d'ascite se reformant aussi rapidement, d'hépatomégalie douloureuse sans cardiopathie et de perturbation des tests hépatiques, surtout le B.S.P., l'hypothèse d'un syndrome de Budd-Chiari est posée. D'autant plus que la laparotomie n'avait rien révélé au niveau des veines porte et splénique. Il ne semble pas y avoir d'atteinte cirrhotique du foie ni de lésion aux organes génitaux.

Une nouvelle laparotomie est suggérée pour une biopsie hépatique, une prise de tension de la veine porte et aussi pour drainage d'ascite. Elle a lieu le 21 octobre 1960. On retire 6000 cc d'ascite. Le foie est augmenté de volume dans son ensemble, dur, lisse et de couleur rouge violacé. Les vaisseaux spléniques et les ovaires sont normaux. La pression de la veine porte a été prise avec un appareil "Twin-niso". Elle était de 11 mm. Hg donc normale (Fig. 1).

La possibilité de faire un shunt porto-cave est écartée vu l'absence d'hypertension portale. Une biopsie hépatique est alors pratiquée et on laisse un drain pour éviter les ponctions d'ascite à répétition.

La tension normale de la veine porte nous fait douter du diagnostic de Budd-Chiari malgré que les signes cliniques et l'évolution soient très en faveur d'un tel syndrome. Le rapport de la biopsie arrive cependant le 25 octobre 1960 pour confirmer le Budd-Chiari.

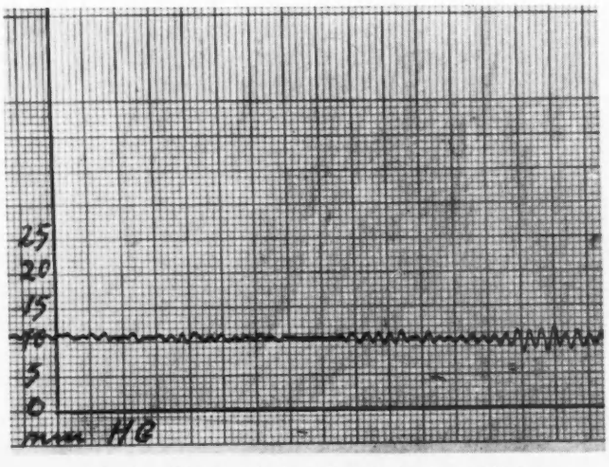

Fig. 1.—Tension de la veine porte (mm. Hg).

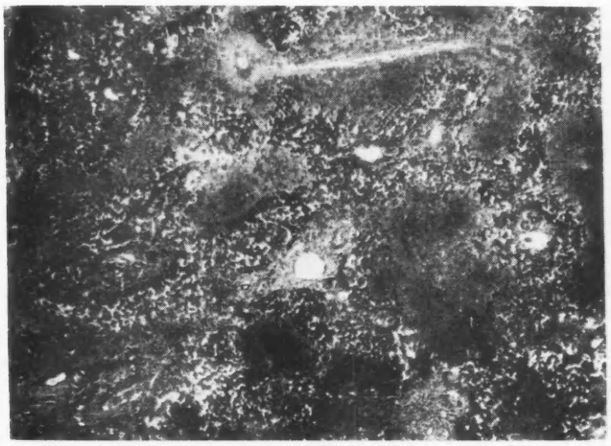

Fig. 2.—Biopsie du foie. Lobules hépatiques refoulés par des zones hémorragiques. Ces zones hémorragiques se situent dans la région centro-lobulaire.

Biopsie hépatique:

Il s'agit d'une biopsie du foie (Fig. 2). Les lobules hépatiques sont refoulés par de nombreuses zones hemorragiques. On aperçoit des placards de globules rouges situés surtout au pourtour des veins centrolobulaires. Ces placards effacent presque complètement les travées hépatiques. Il peut s'agir de zones d'infarctus, à la suite d'une oblitération de vaisseaux sanguins (veines sus-hépatiques). Légère sclérose à la périphérie.

Pendant tout ce temps, le traitement médical se poursuit: un régime riche en hydrates de carbone, en protéines et pauvre en lipides; des électrolytes par voie endoveineuse de la vitaminothérapie; des extraits de foie total et des anaboliques par injections intramusculaires. Le 26 octobre 1960, la patiente décède à la suite d'une chute de tension artérielle rapide et irréversible soit 36 jours après son arrivée à l'hôpital.

Autopsie:

Il s'agit du cadavre amaigri d'une femme de 39 ans dont la peau est sèche.

La cavité péricardique contient 15 à 25 cc de liquide jaune citrin. La valvule mitrale mesure 9.5 mm., l'aortique 7, la tricuspide 11.5 et la pulmonaire 7. Toutes sont libres de lésions macroscopiques. Le cœur pèse 360 g. Les vaisseaux coronaires sont perméables sur tout leur trajet. L'aorte ne présente aucune plaque d'athérome. Au niveau de la veine cave inférieure on note la présence d'un caillot qui part de l'oreillette droite et qui descend jusqu'en bas de la bifurcation de la veine hépatique. Il s'agit d'un caillot post-mortem.

Le poumon droit pèse 240 g. et le gauche 200. Tous les deux sont de coloration rosée au niveau des lobes supérieurs. Toutefois les lobes inférieurs sont collabés et nous laissent croire, à cause de leur coloration rouge foncé, à une atélectasie ante-mortem. Leur tranche de section ne laisse écouler aucun liquide.

A l'ouverture de l'abdomen on trouve un liquide d'ascite de coloration rosée. L'estomac et le côlon sont très dilatés. Le foie apparaît augmenté de volume, de consistance ferme, et de coloration gris-verdâtre. Dans son ensemble le petit intestin ne montre aucune lésion macroscopiquement visible.

Le pancréas pèse 140 g.; il est de consistance ferme mais ne présente aucune lésion macroscopique.

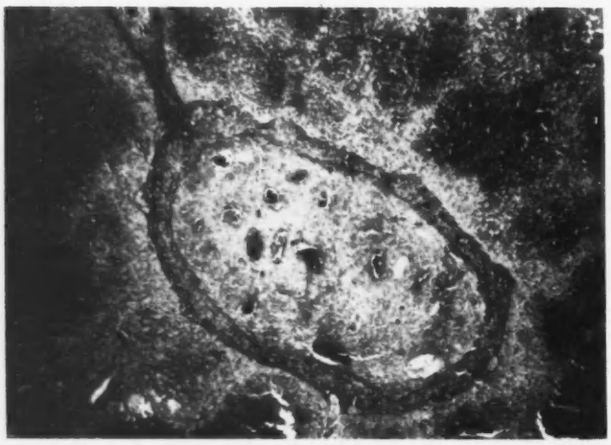

Fig. 3.—Thrombus organisé dans une veine sus-hépatique de moyen calibre. A noter les néo-vaisseaux dans le stroma du thrombus.

Fig. 4.—Fort grossissement d'une partie de veine sus-hépatique montrant la paroi de la veine et le thrombus organisé dans la lumière.

La rate de 190 g., est de coloration rouge foncé et de consistance ferme. Elle est légèrement augmentée de volume et sa tranche de section montre un piqueté grisâtre.

La vésicule biliaire ne contient aucun calcul. La bile est de coloration vert foncé.

Le foie atteint 1675 g.; la capsule de Glisson est épaissie. L'organe est de consistance ferme et à la palpation semble granuleux. Après ablation du caillot post-mortem situé dans les veines sus-hépatiques, nous trouvons que celles-ci sont perméables. La tranche de section laisse écouler en abondance un sang épais et noirâtre. Le parenchyme présente deux zones nettement différenciées, l'une correspondant à un foie granuleux en petits grains de sable, l'autre à un foie infarci. En effet, le bord supérieur du foie montre une coloration rouge sombre qui tranche nettement sur le parenchyme environnant. Il s'agit d'une zone d'infarctus. Dans l'ensemble, l'image est celle du "foie muscade".

Les deux reins pèsent 150 g. chacun et ne portent aucune lésion macroscopique.

Examen microscopique du foie:

A différents endroits on aperçoit dans le parenchyme hépatique des veines identifiées par les limitantes élastiques et la tortuosité de leur lumière. La plupart de ces veines ont une lumière complètement bouchée par une formation conjonctive dans laquelle on discerne des petits néo-capillaires. Autour des vaisseaux thrombosés se trouve un infarcissement du parenchyme hépatique. En effet, un plus fort grossissement révèle de nombreux globules rouges qui étouffent les travées hépatiques. A noter que les lésions d'infarcissement se manifestent surtout à la périphérie de la veine centro-lobulaire. Au niveau des espaces-portes, les travées hépatiques sont plus ou moins normales.

En somme, c'est l'image histologique d'une nécrose et d'un infarcissement hépatique secondaire à une thrombose des veines sus-hépatiques (Budd-Chiari). A noter qu'il n'existe pas de thrombus dans la lumière des grosses veines sus-hépatiques (Figs. 3 et 4).

ETIOLOGIE:

Selon Fruhling, le syndrome de Budd-Chiari doit comprendre "toutes les obstructions des veines sus-hépatiques, qu'elles soient primitives ou secondaires, dues à des affections locales ou la manifestation d'affections générales, qu'elles aient ou non donné des signes cliniques caractéristiques".

Il y aurait ainsi des formes primitives et des formes secondaires:[9]

A *Formes primitives* (Détrie):

Ce sont les formes les plus rares. Le processus serait une endo-phlébite oblitérante primitive au niveau des veines sus-hépatiques. Diverses causes ont été invoquées:

1. Endophlébite toxique, éthylique, alimentaire, gravidique, arsénicale, infectieuse, allergique, fœtale, etc.
2. Thrombo-phlébite banale, dont la cause efficiente est l'infection et la cause favorisante, le ralentissement circulatoire post-hépatique.
3. Endophlébite traumatique: le foie suspendu par les veines sus-hépatiques peut amener des torsions de celles-ci déterminant une thrombo-phlébite oblitérante.

B *Formes secondaires:*

Par compression ou hyper-coagulabilité:

(a) *Affections intra-hépatiques*: abcès unique ou multiple, tumeurs primitives ou métastatiques, gomme syphilitique, kyste hydatique, actinomycose, cirrhose.

(b) *Affections péri-hépatiques:* péri-hépatite, thromboses et processus néoplasiques de la veine cave inférieure,[5] péritonite, péricardite, tumeurs du rein ou de la surrénale, extension d'une thrombose de la veine porte.

(c) *Maladies polythrombosantes:* polycythémie, leucémie, anémie à cellules falciformes, syndrome de Marchiafava-Micheli, purpura thrombo-cytopénique.

C *Divers:* intoxication par la sénécine, malnutrition tropicale, infections générales (septicémié à colibacille), Budd-Chiari du nourrisson.

On constate donc la grande variété des états pouvant amener la thrombose des veines sus-hépatiques et c'est pour cette raison qu'il faut conserver le terme de "syndrome".

PATHOGÉNIE:

Le foie possède un double apport sanguin par l'artère hépatique et la veine porte. Les deux courants se rejoignent dans les sinusoïdes et il y a mélange des deux sangs à ce niveau. Les sinusoïdes se drainent dans les veines centro-lobulaires qui elles-mêmes se jettent dans les veines sus-hépatiques et la veine cave inférieure. Pour s'oxygéner, le foie doit puiser principalement dans le sang portal qui a une pression très basse qui contient très peu d'oxygène. Ainsi les cellules centro-lobulaires, en étant les plus éloignées de la source d'apport de sang oxygéné, sont les plus susceptibles de souffrir d'anoxie. Les principaux facteurs prédisposant à la thrombose seraient: des anomalies congénitales des veines sus-hépatiques,[13, 15] l'obliquité de la jonction des veines sus-hépatiques avec la veine cave,[13] la torsion des veines sus-hépatiques dans la station debout, la stase dans la veine cave inférieure comme conséquence de l'élévation de la pression intra-thoracique durant l'inspiration.

Les localisations habituelles des thromboses sont à la jonction des veines sus-hépatiques avec la veine cave inférieure. Il s'agit soit d'une thrombose de l'orifice des veines sus-hépatiques; soit de l'extension aux veines sus-hépatiques d'une thrombose de la veine cave inférieure. L'occlusion primitive des veines dans le parenchyme hépatique et même seulement des petites veines sus-hépatiques sans atteinte des troncs principaux (comme dans le cas rapporté ici) est excessivement rare.

Partant de ces constatations, nous pouvons tenter d'expliquer la production rapide d'ascite dans le Budd-Chiari. Selon les concepts actuels, les facteurs en jeu sont:

1. *l'hypertension portale*: ce facteur est de plus en plus mis en doute. L'hypertension hydrostatique portale seule ne cause pas fréquemment d'ascite;

2. *l'hypertension des veines hépatiques*: ce serait la principale source de l'ascite dans le Budd-Chiari. Expérimentalement, Mallet-Guy de Lyon[16, 17] a prouvé le grand pouvoir de production d'ascite par la ligature des veines hépatiques sans hypertension portale concommitante. Il y aurait alors transsudation liquidienne à travers la capsule de Glisson;

3. *la baisse de la pression osmotique* des protéines colloïdales du plasma:

4. *les facteurs rénaux et hormonaux* en relation avec l'effet de l'hormone antidiurétique et de l'hyperaldostéronisme secondaire.

ANATOMIE PATHOLOGIQUE:

A. *Macroscopiquement*:

Dans les formes aiguës, le foie est congestionné et volumineux. Sa surface est lisse et violacée. A la coupe, le parenchyme est foncé, prenant l'aspect du "foie muscade".

Du sang s'écoule à la tranche de section et l'on peut apercevoir des thromboses au niveau des ramifications des veines sus-hépatiques. Les lésions peuvent parfois prendre un aspect cunéiforme si la thrombose est restée localisée à quelques-unes seulement des veines sus-hépatiques.

Dans les formes chroniques, on peut rencontrer tous les aspects, soit du gros foie congestif jusqu'au foie fibreux et atrophique. On a signalé la relation fréquente de l'hypertrophie du lobe de Riedel dans les cas où les thromboses n'atteignent pas toutes les veines sus-hépatiques.

B. *Microscopiquement*:

Les formes aiguës sont caractérisées par une congestion centro-lobulaire intense avec distension de la veine si elle n'est pas thrombosée. Les cellules hépatiques de cette zone, dégénèrent, s'atrophient et sont remplacées par une nappe de sang.

Dans les formes chroniques, on remarque de la fibrose centro-lobulaire. On retrouve également des thrombi organisés dans les veines sus-hépatiques. Quelquefois, surtout dans les cas chroniques, ces thrombi peuvent être reperméabilisés. Sur le même foie, différents stades peuvent se superposer ou s'intriquer. Les parois vasculaires sont parfois normales, souvent elles sont le siège de proliférations endothéliales avec fibrose de l'intima.

La maladie veino-occlusive du foie décrite par Stuart et Bras[24] de la Jamaïque, frappe surtout les enfants mal nourris des Indes occidentales, des Barbades et de l'Afrique du Sud. Elle serait causée par un empoisonnement au séneçon et est caractérisée par des thrombi des petites veines hépatiques sans atteinte des troncs principaux. En dehors de cette forme particulière, on a rapporté très peu de cas où les thrombi se localisaient seulement dans les petites veines hépatiques.[3, 14, 22]

CLINIQUE

On rencontre le syndrome dans les deux sexes, avec la même fréquence. Il peut arriver à tous les âges, de la naissance à 70 ans, avec une fréquence plus grande entre 20 et 40 ans. On doit distinguer deux formes cliniques, l'aiguë et la chronique.

A. *Forme aiguë*:

Dans la forme aiguë résultant d'une obstruction subite des veines hépatiques, le début est brutal avec une douleur à l'hypocondre droit irradiant dans le dos et les épaules, des nausées et des vomissements. L'ascite apparaît rapidement. On constate une hépatomégalie douloureuse accompagnée parfois d'un léger sub-ictère. La rate peut-être augmentée de volume et la circulation collatérale est rare et située à la région thoracique basse. L'œdème des membres inférieurs est discret et tardif et apparaît quand il y a atteinte simultanée de la veine cave inférieure. Le collapsus est souvent persistant et conduit à l'oligurie et l'anurie. La mort survient en une à quatre semaines par le coma hépatique, l'anurie ou le choc.

B. *Forme chronique*:

Dans la forme chronique consécutive à une occlusion veineuse progressive ou à des épisodes thrombotiques répétés, le début est insidieux avec des douleurs abdominales vagues, une ascite volumineuse et rebelle, une hépatomégalie graduelle, une circulation collatérale superficielle plus marquée que dans la forme aiguë et située aux régions sus-ombilicale et thoracique basse et d'une façon très évocatrice autour de l'appendice xyphoïde. La splénomégalie est plus fréquente, de même que l'œdème des membres inférieurs. Rarement le foie est petit, atrophique et scléreux après une longue période d'hépatomégalie congestive. Le réflexe hépato-jugulaire est absent. L'évolution est chronique, avec des exacerbations. La mort survient en six mois par coma, infection intercurrente, hémorragie digestive. Quelques cas de survie prolongée ont été signalés.

DIAGNOSTIC:

On a dit que diagnostic du syndrome de Budd-Chiari pouvait être évoqué devant un tableau de cirrhose cardiaque sans cardiopathie. Cependent, certains examens complémentaires ont démontré leur utilitié.

L'hyperglobulinémie, l'allongement du temps de prothrombine, la réduction du cholestérol estérifié, l'élévation de la bilirubinémie n'ont pas plus de valeur spécifique que la leucocytose avec légère polyglobulie. Par contre le test de rétention de brome-sulphone-phtaléine semble le plus caractéristique. Précocement le taux de rétention est très élevé "comme si la thrombose des veines hépatiques était la lésion qui nuisait le plus à l'excrétion de B.S.P." La ponction biopsique du foie a une grande valeur si elle montre les images caractéristiques de thrombose centro-lobulaire. L'examen du liquide d'ascite peut aider à localiser le lieu de la thrombose. Si elle siège sur la veine cave entre le foie et le cœur, l'ascite est très riche en albumine. Au contraire si l'atteinte est à l'intérieur du parenchyme hépatique, le taux d'albumine est beaucoup moins élevé selon Caroli.

La radiologie peut contribuer à l'établissement du diagnostic par la splénoportographie avec manométrie qui démontre une hypertension portale et la liberté du système spléno-portal. La cavographie peut aussi être utile en cas de thrombose associée de la veine cave inférieure.

Le diagnostic différentiel doit se faire avec la cholécystite, l'hépatite, la péricardite constrictive, la cirrhose, la thrombose de la veine porte et la thrombose de la veine cave. La présence concomitante de ces deux dernières conditions est toujours possible.

TRAITEMENT:

On ne peut en parler très longuement vu le peu de succès rapporté jusqu'ici. Le traitement médical consiste en un régime de support et la surveillance des complications: l'ascite, les déséquilibres électrolytiques, les hémorragies digestives et le coma hépatique. Les anti-coagulants se sont révélés inefficaces. Les diurétiques ne parviennent pas à maîtriser l'ascite. Peut-être, les fibrinolytiques récemment introduits dans le traitement des thromboses représenteront-ils une acquisition précieuse.

Le traitement chirurgical lui aussi n'est que palliatif. Les diverses interventions proposées visent toutes à diminuer l'hypertension portale soit par la ligature de l'artère hépatique, soit par une anastomose porto-cave ou spléno-rénale. De celles-ci, l'anastomose porto-cave semble la plus logique malgré que très peu de succès aient été rapportés jusqu'à maintenant avec cette méthode.

DISCUSSION:

Nous croyons que l'intérêt de cette publication repose sur deux points: d'abord l'aspect inhabituel des lésions hépatiques, ensuite la preuve apportée chez l'humain à une théorie sur le mécanisme de formation de l'ascite jusqu'ici démontrée seulement chez l'animal.

Nous n'avons retrouvé que trois cas semblables dans la littérature: celui de Salvesen et Torgesen,[22] celui de Kubicki, Karlinska et Sujkowska[14] et enfin celui de Batzenschlager, Bockel et Kempf.[3] L'aspect anatomo-pathologique est en tout point identique. Les veines sub-lobulaires étaient obstruées complètement par des thrombi partiellement ou complètement organisés. L'absence de thrombose dans les veines hépatiques principales est remarquable contrairement à la plupart des cas rapportés. Aucun facteur prédisposant n'a pu être mis en évidence.

L'autre point intéressant est la présence d'une ascite considérable, se reformant rapidement malgré l'absence d'hypertension portale vérifiée directement. Nous touchons alors un problème très discuté actuellement: l'importance de l'hypertension portale dans la genèse de l'ascite. Mallet-Guy et ses collaborateurs[16, 17] et plus tard Aiello, Enquist et collaborateurs,[1] ont réalisé expérimentalement chez le chien, des Budd-Chiari en ligaturant les veines sus-hépatiques. Ils ont constaté une formation d'ascite rapide avant même l'élévation de la tension portale.

Nous n'avons pas trouvé dans la littérature de cas de ce syndrome où la tension portale était normale. Peut-être n'était-elle pas prise au tout début de la maladie. Il semble que dans cette lésion, la tension portale soit normale au début et s'élève assez rapidement par la suite.[19] Il est très intéressant de rapprocher notre cas des expériences de Mallet-Guy car nous avons un Budd-Chiari avec ascite abondante, sans hypertension portale. Il nous est donc permis de conclure partiellement avec lui que:

1. "l'ascite dite mécanique n'est pas le fait de l'hypertension portale" et (2) "qu'elle est cependant bien due à un facteur mécanique, la congestion veineuse hépatique, expérimentalement réalisée (constatée cliniquement dans le cas rapporté) par sténose post-hépatique".

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SUMMARY

The authors report a case of Budd-Chiari syndrome resulting from primary thrombosis of the small hepatic and sublobular veins, without involvement of the large hepatic veins and without portal hypertension. The etiology, pathogenesis, clinical and anatomicopathological aspects, the diagnostic procedures and the therapeutic possibilities have been reviewed. In the opinion of the authors the mechanical ascites is not a result of portal hypertension, but rather is secondary to the venous hepatic congestion from posthepatic stenosis. In this regard, the views of Mallet-Guy concerning the mechanisms of ascites are reviewed.

EXTRAPYRAMIDAL SYMPTOMS ASSOCIATED WITH THE ADMINISTRATION OF TRIFLUOPERAZINE:

REPORT OF A CASE TREATED WITH DIPHENHYDRAMINE

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BECAUSE of the increasingly widespread use of the phenothiazines as tranquillizing and antiemetic agents, various toxic reactions to these preparations have been reported. The following paper reports the occurrence of severe extrapyramidal symptoms associated with the oral administration of trifluoperazine (Stelazine) and the rapid relief of symptoms with diphenhydramine (Benadryl).

A 20-year-old third-year university student was admitted to hospital with general malaise, sore throat, enlarged glands on the right side of her neck and moderately severe nausea. She had been seen a few days before admission because of these complaints and was treated with oral penicillin with no appreciable effect. Examination on admission revealed a young, ill-looking, white woman with a temperature of 102° F. She had an acute pharyngitis, presumably of streptococcal origin. The cervical lymph nodes were enlarged bilaterally, but were more marked on the right side. The remainder of the physical examination was negative. Another physician treated the patient with erythromycin 250 mg. four times daily and gave trifluoperazine (Stelazine) 2 mg. three times daily before meals for the control of nausea.

I first saw the patient on the evening of the second hospital day because of marked restlessness and muscular twitching with a tremor of both hands. Examination revealed, as well as these symptoms and signs, involuntary protrusion of the tongue and marked muscle spasm of her back with severe hyperextension of the trunk. The most striking feature of the trunk involvement was its intermittency. The face was expressionless with drooping of both corners of the mouth, and facial twitching was noted. The deep tendon reflexes were hyperactive and equal bilaterally, the sensorium was normal and there was no oculogyric crisis. On two occasions marked opisthotonos occurred. The patient constantly changed position from lying to sitting to lying, claiming that this afforded some relief. Previous descriptions[1, 2] of the side effects of phenothiazine administration indicated that the parenteral administration of diphenhydramine was most effective in relieving the extrapyramidal symptoms associated with other phenothiazines (prochlorperazine and perphenazine). This patient was given diphenhydramine 50 mg. intramuscularly and within 20-30 minutes she had a marked relief of symptoms. Within one hour all symptoms had subsided with the exception of some muscle twitching of the face. Another 50 mg. of diphenhydramine was given by mouth, the administration of trifluoperazine was discontinued and there was no recurrence of symptoms. The patient remained asymptomatic for the remainder of her hospital stay.

SUMMARY

Apparently most reactions of this type tend to occur with higher dosage levels;[3] in this patient a total of 10 mg. of trifluoperazine was given over a period of 36 hours. The occurrence of severe extrapyramidal symptoms associated with the use of trifluoperazine and rapidly relieved by the use of diphenhydramine is reported.

The exact mechanism of action of this established antihistaminic drug is unknown.

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TUBERCULOSIS IN ONTARIO

THE introduction of antimicrobial drugs in the treatment of tuberculosis in the last 15 years has had a pronounced effect on the mortality from this disease. The fall in mortality which was evident for many decades became greatly accelerated. In Ontario, in 1960, the mortality rate was 2.6 per 100,000, not only the lowest on record in that province, but one of the lowest in the world. The mortality for Canada as a whole was 4.6 per 100,000 in the same year. Tuberculosis need no longer be a fatal disease and some of the deaths that it causes at present may well represent a breakdown in diagnostic and therapeutic facilities.

Morbidity from tuberculosis is still relatively high. As reported elsewhere in this Journal, 2030 active cases of tuberculosis were recorded by the newly established Provincial Case Register in 1960 —one active case for each 3000 citizens of the province. While there are indications that the morbidity is also falling, we have not yet reached the stage in which tuberculosis can be considered from either a public health or a clinical standpoint as a negligible problem. The fact that some sanatoria have closed and others have an appreciable proportion of empty beds is due in no small part to the changing pattern of treatment rather than to the decline of morbidity.

The decline in tuberculosis experienced in Ontario is the result of the high and rising standard of living and of the great efforts that have been made in that province for many years toward the thorough control of this disease. Modern drug treatment accelerated this process. The underlying mechanism of this decline appears quite simple: tuberculous infection has become relatively uncommon. Mass surveys conducted in the last three years reveal that less than one-fifth of the total population of Ontario shows a positive tuberculin reaction—a far cry from the time when tuberculous infection was thought to be universal among adults. Primary infection with tubercle bacilli is becoming relatively uncommon, and most of our tuberculin-positive population were infected a long time ago. This is the principal reason for the current predominance of tuberculosis among the elderly, particularly among older men.

The present epidemiological situation, while satisfactory, holds certain dangers. The principal hazard relates to the fact that such a large segment of the population is tuberculin-negative and, therefore, devoid of the benefits of acquired immunity. If present living conditions and present tuberculosis control measures are maintained, tuberculosis will no doubt continue to decline. If, however, there is a breakdown in one or other of these two factors, tuberculosis could again become a very common health hazard. The other danger relates to the emergence of resistant tubercle bacilli. Close to 10% of previously untreated patients reveal full bacterial resistance to at least one of the three main drugs used in the treatment of tuberculosis.

Efficient tuberculosis control measures will therefore have to be maintained and even strengthened in spite of the decline in tuberculosis rates. Today a patient with positive sputum is of greater importance as a source of infection than 30 years ago, as most of the people with whom he comes into contact are tuberculin-negative. Notification of tuberculosis is one of the prerequisites of good control, and it is discouraging to learn that only 60% of newly discovered cases are notified.

Treatment of tuberculosis is prolonged, and must be well supervised and uninterrupted if the emergence of resistant bacilli is to be prevented. Resistance studies should be carried out in all cases of tuberculosis with positive bacteriology; before the results of such studies become available for individual patients, treatment with three antituberculous drugs rather than with two should be instituted, lest by the time the organisms are proved to be resistant to one of the two drugs the sensitivity to the second drug has been lost.

The patient with active tuberculosis should whenever possible have his treatment initiated in a sanatorium. Physicians undertaking treatment on an ambulatory basis must make certain not only that the patient has been properly assessed and has received adequate antimicrobial therapy but also that spread of infection has been prevented.

Although protective vaccination against tuberculosis might not constitute a substantial contribution in the community in which primary infection is uncommon, nevertheless its use should be continued among contacts of cases of tuberculosis, nurses, and similar high-risk groups. Extension of preventive vaccination to older school children could protect them through the susceptible years of adolescence and young adult life, and could act as a form of insurance against recrudescence of tuberculosis should any calamity affect our way of life.

The present satisfactory situation and the hopeful trends in tuberculosis control, morbidity and mortality are a result of the interaction of multiple socio-economic and medical factors; this unstable equilibrium might easily be upset.

Tuberculosis is still the most important health problem in many parts of this changing world; at present it is possible to control or perhaps even to eradicate this disease in one country; will this be possible in the much smaller world of tomorrow?

OUR GOOD NAME

Who steals my purse steals trash; 'tis something, nothing;
'Twas mine, 'tis his and has been slave to thousands;
But he that filches from me my good name
Robs me of that which not enriches him
And makes me poor indeed.

AS usual, the Bard had a word for it and the occasion to quote Othello arises from the spectacle of a large professional Association in a neighbouring republic suffering in apparent embarrassment because its good name has been used to enrich, at least temporarily, the manufacturers of a commercial product. This embarrassing episode arose because a unit of the Association concerned saw fit to grant "recognition" to a dentifrice.

During the controversy that followed the announcement that "dentifrice X" had provided "reasonable evidence of usefulness and safety", the professional Association concerned held that "recognition" did not imply "endorsement". However, despite this disclaimer, the effect was to give "dentifrice X" a tremendous advantage in the marketplace.

Similarly, The Canadian Medical Association may be placed in a practical dilemma from time to time by pressure to "recognize" specific therapeutic "advances", particularly those that have a wide application and are susceptible to commercial development. Usually, it does this through its publications, by drawing attention to those agents that are considered to constitute definite improvements in therapy. By so doing, impetus is given to their widespread use by practising physicians.

When a professional organization has a committee which evaluates the therapeutic effectiveness of new products or devices, the dilemma is heightened; a favourable decision by such a committee has the strength of an endorsation by the profession. The Canadian Medical Association does not have a council or committee to evaluate therapeutic agents and is unlikely to in the near future, because of the number of personnel, the time, and the extensive laboratory facilities required. Pronouncements on the efficacy of a drug or a method of treatment are most appropriately made by those who have carried out careful scientific studies of the agent concerned. These pronouncements will be incidental to or embodied within the text of original scientific articles and will, except when acknowledging assistance from the manufacturer, describe drugs by their chemical or non-proprietary names. This process allows the professional organization to avoid the suggestion of favouring one manufacturer over another but leaves the Association, through its physician-authors and editors, free to call favourable attention to a promising mode of treatment through editorial comment.

The Canadian Medical Association not infrequently receives requests for the endorsement of drugs, appliances, procedures, television scripts, advertising copy and all manner of promotional devices. Some of these approaches are very seductive and they are represented as showing the profession's support of a worthy educational effort or a public service which might be regarded as a means of bringing our name to public attention in a favourable light. Sometimes a thinly veiled *quid pro quo* is involved, and our approval may be sought at the price of a scholarship or monetary support of a project. The issues are often not entirely clear-cut. Many of the approaches are blatantly commercial and it is possible to dispose of these by saying that the C.M.A. does not undertake to test, approve, endorse, guarantee, accept or recognize, foods, drugs, cosmetics, appliances or methods or theories of treatment.

The common underlying reason for these requests is, of course, to use the name and prestige of our Association for profit. Our Code of Ethics applies the principle to individual physicians in the following words: "It is precisely because he is a physician that his advocacy has extra market value. In thus advertising a commodity, he presumes to sell that which is not his to sell, the common tradition and inheritance of reputation, esteem and standing of the whole profession." It appears to be seemly that as an Association we should follow the ethical principles which guide our individual members and resolutely refuse to barter our good name.

A.D.K.

EXTERNAL CARDIAC MASSAGE

CARDIAC arrest due to ventricular fibrillation or asystole is a common mode of death in patients with acute myocardial ischemia and infarction. Although pathological studies have shown that the myocardial damage in many of these patients is comparatively slight, it is still widely assumed that they have such severe heart disease that resuscitation by cardiac massage would be almost certain to fail.

As Julian[1] remarks, there is little point in attempting resuscitation when shock or severe cardiac failure has preceded cardiac arrest, and when the

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presence of severe myocardial damage may therefore be presumed. On the other hand, in the absence of these complications, it is possible for treated patients to maintain a blood pressure level compatible with survival, without severe decompensation.

A year ago, Kouwenhoven, Jude and Knickerbocker[2] described a technique for cardiac massage without opening the chest. Reports since then have confirmed that this procedure is generally successful in maintaining an effective circulation.[3, 4] The introduction of closed-chest cardiac massage constitutes a major advance in the treatment of cardiac arrest, especially in medical (in contrast to surgical) cases. Because external cardiac massage can be initiated immediately, it shortens the time between the diagnosis of cardiac arrest and the start of treatment; external cardiac massage does not involve a surgical procedure; and by maintaining an effective circulation it allows time for additional equipment and personnel to be mobilized.

External compression over the lower sternum effectively massages the heart owing to the fixation of that organ in the mediastinum and the flexibility of the chest wall in the unconscious patient. It should be carried out as follows: The lower sternum should be sharply compressed, with a forceful jerky movement, 60 times a minute. The patient should be supine and on a hard surface. The force required may have to move the sternum as much as 3 or 4 cm. towards the vertebral column. The carotid and femoral pulses and the size of the pupils should be observed to judge the effectiveness of the cardiac massage. This procedure provides some pulmonary ventilation but it is preferable, in addition, to institute mouth-to-mouth breathing or positive pressure respiration through an endotracheal tube.

Electrical defibrillation is usually necessary in the presence of ventricular fibrillation. For use with closed-chest cardiac massage it must be able to deliver 780 volts to the chest wall.[1] Since ventricular fibrillation cannot be diagnosed except by electrocardiography or by direct inspection of the heart, an electrocardiograph should be obtained as soon as possible. Many shocks from the defibrillator may be required. As well, procaine amide may prove a valuable addition to cardiac massage and defibrillation in the treatment of ventricular fibrillation.

Serious complications may sometimes follow closed-chest cardiac massage.[1, 5, 6] These include fractured ribs, hemothorax, marrow embolism, laceration of the liver and hemopericardium. The frequency of these complications has been found to decrease with growing experience in the technique. The principle of applying pressure to the sternum *only* is important to avoid the traumatic complications of this procedure. Since the layman or first-aid worker may sometimes have difficulty in distinguishing between cardiac arrest and simple syncope, it would be dangerous for such personnel to carry out this procedure as a routine first-aid maneuver. As an editorial[7] in the *New England Journal of Medicine* puts it: ". . . If the police and firefighter are to be instructed in the use of this technic, they must also be taught *when* to use it as well as *how* to use it. Otherwise, those who are apt to faint in public places may suffer cracked ribs and torn livers for their indiscretion."

It has been recommended[1] that certain hospital patients thought to be at risk from ventricular fibrillation or asystole should have their cardiac rhythm constantly monitored. The provision of appropriate apparatus would not be prohibitively expensive if these patients were admitted to special intensive-care wards staffed by suitably experienced personnel throughout the 24 hours of each day.

Even the occasional success with external cardiac massage makes worth while the attempt to resuscitate a patient with myocardial infarction in whom cardiac arrest suddenly develops.

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PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

GENITAL TUBERCULOSIS

The fourteenth German Gynæcological Congress, held at Munich from June 7th to 10th, discussed as the chief theme the relation of tuberculosis to the female genital organs. The discussion was opened by Jung, of Gœttingen, who stated that one and a half to two of all autopsies in females showed the presence of tuberculosis of the genitalia. This condition was usually hæmatogenous in origin, though it might arise from peritoneal extension after the breaking down of glands. It was seldom primary, and while a descending infection had been proven, ascending infection, while possible, had not been definitely proven, though extension by continuity could not be excluded. The tubes were most frequently infected in this form of the disease, probably in ninety per cent. of the cases. The salpingitis could not be differentiated into acute and chronic. Healing had been noted, and occasionally bacilli had been found in the secretions, but in the majority of cases the infection was mixed. Tuberculosis of the uterus was usually an extension from the tubes, and attention was called to the cauliflower-like growth upon the portio-vaginalis of the cervix, which might be confused with carcinoma. The ovaries were rarely affected, probably on account of the thick surface covering, though a hæmatogenous infection of the ovary was not impossible nor was a similar infection of the vagina and vulva, which on account of the character of the epithelium usually escaped.—Editorial, *Canad. M. A. J.*, 1: 1200, 1911.

Letters to the Journal

". . . NOTHING HUMAN INDIFFERENT TO ME"

To the Editor:

Your leading editorial of November 4 (*Canad. M. A. J.*, 85: 1056, 1961) is most intriguing. It is also enlightening because of the rather lengthy history of parapsychology. The absence of any mention or recognition of Rhine and associates makes one wonder whether this was forgotten, an oversight or deliberate. Surely the amount of work done at Duke University warrants critical review with sufficient reporting.

Perhaps others of your readers noticed this omission also.

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MEDICAL DISCIPLINE

To the Editor:

Self-discipline has always been, and remains today, a primary attribute of any true profession. In medicine, we are officially entrusted and directed by the people through the legislature to regulate the standards and quality of practice. This discipline is taught to the newest student and we recognize it repeatedly through our careers. We demand of each other consultations, we arrange for hospital accreditation, we form countless committees to check ourselves and we establish incentives to high standards in the College of General Practice and in the Royal College of Physicians and Surgeons. Nor have we lacked outspoken critics who will not be muzzled. Almost 60 years ago, Sir William O. Priestley delivered an address "On Over-operating in Gynecology" (*Brit. M. J.*, 2: 284, 1895). In this address, he pointed out the great advances which had recently been made in gynecology and midwifery but warned of certain dangerous trends in the practice of the day. To illustrate the tone and sincerity of his remarks, I quote from his summing-up:

"I venture to speak strongly on these matters not because I am reactionary or opposed to real progress in our art; I render all honour to the pioneers of true progress, and every useful and proved innovation will always find in me an ardent supporter. As I now, in some sort from seniority, stand outside the circle of strife, I can calmly survey the whole horizon of work, and feel a desire to assist my confrères in attaining a judicial standard of what is right to be done, and what is best left undone—and the motto of all should be, *Primo non nocere*—at least do no harm."

One cannot but contrast this humble but firm and sincere admonition with the recent sensational outbursts of some of our senior colleagues who chose to use the platform of the public press to address us. The implication, clearly, is that the patient is a better judge of the proper medical or surgical treatment than the physician.

Anyone has the right to seek or avoid medical care. But surely the patient who consults his physician does so because he judges himself incapable of diagnosing and treating, and believes his chances are better when he asks for help from one whose skill in these matters he believes to be greater than his own. The layman, then, *does not* expect to judge on the merits of any diagnosis or treatment. This is not to say that he does not expect to have explained the implications of a diagnosis and proposed treatment, for he too possesses human intelligence, and success will depend on his understanding and co-operation.

But the fact remains that the public expects us to keep our house in order and *does not* wish to propose to do this for us. It follows that we should not ask the public to do so. Our discipline can only work from within—we are directed by law and conscience to exercise this duty within our body corporate. In 1895 Priestley performed such an act of *internal* discipline. Let us hope that in future our senior colleagues will exercise this duty in a similar high-minded fashion.

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Halifax, N.S.

MEDICAL NEWS IN BRIEF

DIGITAL COMPUTER AS AN AID TO DIFFERENTIAL DIAGNOSIS

A study was undertaken to determine the feasibility of employing an electronic digital computer to handle data pertinent to differential diagnosis. M. Lipkin *et al.* (*Arch. Int. Med.*, 108: 56, 1961) compared the symptoms, physical signs and laboratory data characterizing 20 hematologic diseases with the data of 49 hospital patients with hematologic diagnoses. The differential diagnosis of each of the 49 patients was written out. Information returned also stated whether all the findings necessary to make a "positive diagnosis" of a disease were present in a hospital case, and the presentation of a differential diagnosis without a "positive diagnosis" resulted in a computer request for further work-up of the case in an attempt to provide all the information required to establish a "positive diagnosis".

After computer analysis of 28 of the cases, the information returned stated that a "positive diagnosis" could be established, and in each case it corresponded to the diagnosis listed for the hospital case. In 13 cases the information returned listed additional items of data

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which would have to be completed in order to complete the differential diagnosis and establish a diagnosis. In six cases the information returned suggested a re-examination of the data in order to establish the diagnosis. In each instance the infomation returned presented an accurate analysis of that particular case.

If the data of the hospital case were correct, the computer could not return an incorrect "positive diagnosis" with the method of analysis used.

The results of the study indicated that computers can aid in obtaining information of value in differential diagnosis. Expansion of the present programs should further test the usefulness of computers in this function.

DIAGNOSIS AND TREATMENT OF ACUTE GAMMA - HEXACHLOROCYCLOHEXANE POISONING IN SMALL CHILDREN

Gamma-hexachlorocyclohexane (HCCH) is a widely used insecticide which does not cause side effects when it is employed with proper precautions. It is highly toxic, however, when ingested or absorbed through the skin. Initial symptoms are restlessness and vomiting, which are soon followed by convulsions and coma. Owing to sympathetic stimulation, marked mydriasis and hyperglycemia are usually present. The tendon reflexes are diminished or absent, and Chvostek's sign may be present. In lethal poisoning death occurs from circulatory collapse.

HCCH is almost insoluble in water but dissolves readily in fat. Therefore the severity of symptoms depends more on the presence of fat in the gastrointestinal tract than on the amount of drug ingested. Poisoning may become manifest following a fatty meal several hours after the drug has been swallowed.

Acute poisoning due to ingestion of HCCH is most likely to occur in small children because of their habit of putting things in their mouths. Stur and Zweymüller (*Deutsche med. Wchnschr.*, 86:1474,1961) report three illustrative case histories of children between 18 and 24 months of age, who all recovered on treatment. The therapy used consisted of induction of vomiting, gastric lavage, a saline laxative, and, in the presence of convulsions, of intravenous administration of calcium gluconate or calcium thiosulfate. Barbiturates may be necessary during the convulsive stage, but they must be used with great care, because they enhance the tendency to severe circulatory collapse. Milk, which is often used as a universal antidote in poisonings, is dangerous and contraindicated.

EFFECT OF PREGNANCY ON SURVIVAL IN HUMAN MELANOMA

Pregnancy data were analyzed in 71 women between the ages of 15 and 39 years, all of whom had histologically proved cutaneous melanoma. All pregnancies which occurred within one year before the diagnosis of melanoma and five years after the diagnosis were noted, and survival of these patients was plotted. The patients were divided into three groups: (1) 30 patients who were pregnant within the six-year period defined; (2) 31 patients who were not pregnant during this period; and (3) 10 patients for whom no history of pregnancy could be obtained.

The five-year survival was slightly higher in the pregnant group than in the non-pregnant group. However, when age and stage of disease at the time of diagnosis were taken into account, White *et al.* (*J.A.M.A.*, 177: 235, 1961) found the five-year survival was equal in the two groups. Deaths from melanoma may occur more than five years after diagnosis and treatment; these later deaths were as frequent in the non-pregnant as in the pregnant group.

Although no deleterious effect of pregnancy on survival of this group of women with melanoma was demonstrated, no statement can be made as to the advisability of pregnancy in an individual case, and since termination of pregnancy is not effective in causing regression of an established tumour, therapeutic abortion is not a reasonable measure in the management of this disease.

"PANHYPOPITUITARISM" DUE TO FAILURE OF THE THYROID TO UTILIZE IODINE

The clinical picture of combined hypofunction of thyroid, adrenals and gonads is usually caused by panhypopituitarism. In rare instances failure of the thyroid to utilize iodine may produce the same symptomatology. This is illustrated by the following case history: An 18-year-old girl was referred for endocrine studies. Her symptoms had begun at the age of 12 years, when she became disinterested, phlegmatic and sleepy. She developed severe constipation and increasing intolerance to cold. Four menstrual periods at the age of 12 were followed by amenorrhea, but breasts and pubic hair developed normally. An attempt at cyclic hormone therapy by a gynecologist was unsuccessful.

Schneider and Frahm (*Deutsche med. Wchnschr.*, 86:1667, 1961) report that, when she was first seen, physical examination revealed mental dullness, normal secondary sex characteristics, cool dry skin, coarse hair, sparse eyebrows, macroglossia, slight enlargement of the thyroid and marked bradycardia. The pertinent laboratory findings were as follows: basal metabolic rate, −24; blood cholesterol, 291 mg. %; radioactive iodine uptake of the thyroid, 75% in 72 hours; serum utilization index, over 15; 24-hour excretion of cortisone, 1.71 mg.; of 17-ketosteroids, 2.74 mg.; and of gonadotropin, 6.6 mouse units. The estrogen effect in the vaginal smear was absent. The sella turcica was normal radiologically, and the bone age corresponded to the patient's chronological age.

The clinical picture was suggestive of panhypopituitarism, but this diagnosis was ruled out because of the increased iodine clearance and the enlargement of the thyroid, and the presence of gonadotropins in the urine. The basic disorder was considered to be a failure of the thyroid to utilize iodine, the hypofunction of the adrenals and gonads being secondary to the hypometabolism.

The results of therapy proved that this assumption was correct. The patient was treated by administration of thyroid hormone, and six months later she began to menstruate. At that time her BMR was +6, and the excretion of 17-ketosteroids and 17-hydroxysteroids was normal and remained so, as long as the patient took her medication.

(Medical News in Brief continued on advertising page 17)

MEDICAL FILMS

THE FILMS listed below are held in the National Medical and Biological Film Library and are distributed by the Canadian Film Institute, 1762 Carling Avenue, Ottawa 3, Ont. The evaluations have been prepared by Canadian specialists in the subjects of the films, under the Medical Committee of the Scientific Division of the Institute, which is headed by Dr. G. H. Ettinger.

The Faces of Depression—1958; sound; black and white; 28 minutes.

Sponsored by Geigy Pharmaceuticals as one in the series "Documenta Geigy".
Produced by Robert Anderson Associates, Ottawa, Ontario.

Description.—This instructional film shows some of the multiple appearances to be found in depressive states. Dr. H. E. Lehmann of the Verdun Protestant Hospital, Montreal, discusses the variety of signs and symptoms encountered. Patients are seen in short interviews designed to bring these out. Where signs are masked, special danger occurs and the depressed state may be hard to recognize. There may be confusion also with intracranial conditions, examples of which are shown.

Appraisal (1959).—The manifestations of depressive states are well shown in the many patients seen throughout the film. It is especially valuable for the emphasis put on depression as a disease seen earliest in the general practitioner's office. Dating is not important; commentary is accurate, interesting and stimulating. Recommended for general practitioners, medical students in clinical years and nurses. Suitable for medical specialists.

Availability.—National Medical and Biological Film Library ($4.50). For purchase apply to: Robert Anderson Associates, Mountain Road, Hull, P.Q.

Sulfonylureas in the Treatment of Diabetes—1956; black and white; 35 minutes.

Sponsored by Hoechst Pharmaceuticals of Canada.

Description.— This film consists almost entirely of interviews with some of the participants in a conference on the sulfonylureas sponsored by the Upjohn Company at the New York Academy of Medical Sciences. A short biographical sketch is given before each interview, and during each, further information is stated in regard to work done in connection with these drugs. Pioneer workers from France, Germany, the Argentine and Canada are seen.

Appraisal (1960).—There is not a great deal of technical content, and the film could have been made more informative by the addition of material designed to make it live up to its title. The purely interview type of technique used limits its instructional use but makes it a historically valuable record. Suitable for specialists interested in the subject and of limited use for medical students in clinical years. Unsuitable for others.

Availability.—National Medical and Biological Film Library (free).

Oral Cancer—The Problem of Early Diagnosis—1953; sound; colour; 31 minutes.

Produced by Audio Productions for the American Cancer Society and the National Cancer Institute, Public Health Service, U.S. Department of Health, Education and Welfare.

Description.—The film begins with a discussion of the importance of early diagnosis of oral cancer, citing five-year cure rates for various areas in and around the mouth and showing the improvement if early lesions only are selected for analysis. The responsibility of the medical and dental professions is stressed and the details of a thorough examination are illustrated. Diagrams show the true glands and the locations of the lymph nodes draining the areas under discussion. The film ends by showing examples of cancer of various oral sites followed by a short discussion of the technique and place of biopsy in this disease.

Appraisal (1961).—This film has excellent technical content, and is accurate, interesting and up-to-date. It was felt, however, that the sequence showing examination of the neck could have been improved by having the examiner at the patient's head and back. Exception was also taken to the use of a punch for obtaining biopsy material. Photography and sound are on a par with others of this excellent series. Recommended for general practitioners, dentists, medical and dental students in clinical years. Suitable for specialists, medical students in pre-clinical years, nurses, technicians. Unsuitable for non-medical audiences.

Availability.—National Medical and Biological Film Library ($4.00). For purchase apply to: American Cancer Society, 521 W. 57th Street, New York 19, N.Y.

Dental X-Ray Equipment—Alteration for Modern Radiation Hygiene—1960; sound; colour; 20 minutes.

Produced by the Council on Dental Research of the American Dental Association with the co-operation of the National Bureau of Standards of the United States Department of Commerce.

Description.—The film opens by mentioning the handbooks on the subject published by the National Bureau of Standards. One in particular is suitable as a supplement to the content of this film.

Though high-speed film is important in reducing patient exposure, the installation of diaphragms eliminates unnecessary radiation. The making, installation and testing of a diaphragm for a short and long cone are demonstrated. The method of testing for adequate filtration of soft radiation is shown, and after determining the inherent filtration the necessary aluminum filter is cut and installed. Tests for leakage are demonstrated, and outdated, unsafe or inadequate equipment is illustrated, as well as measures for correction.

Appraisal (1960).—The film is intended to stimulate dentists and other users of x-ray equipment to obtain the handbooks and make whatever alterations are necessary to minimize radiation hazard. The film, though up-to-date, interesting and stimulating, does not provide all the information necessary to make the alterations. Recommended for dentists, medical practitioners using x-ray apparatus, and radiological and dental technicians. Suitable for general scientific audiences. Unsuitable for others.

Availability.—National Medical and Biological Film Library ($4.00). For purchase apply to: Office of Technical Information, United States National Bureau of Standards, Washington 25, D.C.

Study in Maternal Attitudes—1959; sound; black and white; 30 minutes.

Produced by Robert Anderson Associates. Sponsored by New York Fund for Children Inc. and City of New York Department of Health.

Description.—This film describes the attitude study project of the Kipps Bay Health Center in New York City and the training given there to doctors and nurses. In the opening sequences the director of the project points out the considerable differences in mothers and some general maternal problems for which they bring their children to the center. The purpose of the project is to study maternal attitudes by questioning along lines that have been proved effective. Portions of seven interviews are seen in an unrehearsed demonstration of this clinic in action.

Appraisal (1960).—The film's purpose is to introduce the technique of observation of the mother's attitude in relation to common pediatric problems. The clarity of presentation makes it a good training film, valuable to anyone dealing with pediatric behaviour problems. Recommended for pediatricians, general practitioners and medical students in clinical years; also Victorian Order of Nurses and public health nurses.

Availability.—National Medical and Biological Film Library ($3.00). For purchase apply to: New York Fund for Children Inc., 104 East 25th St., New York 10, N.Y.

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MEDICAL MEETINGS

UNIVERSITY OF WESTERN ONTARIO HOMECOMING MEDICAL CONFERENCE

On Friday, October 22, under the sponsorship of the Medical Class of 1951, the first University of Western Ontario Postgraduate Homecoming Medical Conference was held in the medical school auditorium. This was a resounding success and the Executive of Meds '51 with its President, Dr. Donald P. Swartz, are to be congratulated. The medical alumni returning on Homecoming Weekend will long remember a memorable day. The entire day was planned and executed in the expectation that this would become an annual meeting of increasingly high calibre which would attract the medical alumni of U.W.O. to return at this season of the year. The theme of the program was planned as a tribute to the work of Dr. Murray Barr, the outgrowth of his original observations and his elaboration of the significance of those observations. Dr. Rodger Rossiter expressed the appreciation of his colleagues at the conclusion of Dr. Barr's major summary address in the afternoon.

Three visiting lecturers participated in the conference: SIR GEORGE PICKERING, Regius Professor of Medicine, Oxford University, who spoke on "Arterial Thrombosis and Embolism"; DR. JOSEPH M. JANES of the Mayo Clinic, whose address was entitled "A Surgical Approach to Vascular Anomalies of the Extremities"; and DR. BROCK E. BRUSH of the Henry Ford Hospital, Detroit, who discussed "Islet Cell Adenomas". One hundred and forty-seven registered for the day-long sessions.

DR. DAVID H. CARR opened the meeting by reviewing the development of the human reproductive system. He emphasized that a knowledge of morphological and experimental embryology is essential to an understanding of the anomalies of the genital system. DR. MURRAY L. BARR then told the fascinating story of the development of the sex chromatin test and what is known of the human cell nuclear chromosomal complement. He clearly indicated that the best diagnostic aid available when faced with a problem involving abnormal development of the reproductive system is the sex chromatin test. Then followed a number of addresses by graduates and staff members of U.W.O., detailing studies along specific lines that have been conducted at that centre. DR. JOHN C. RATHBUN spoke on the adrenogenital syndrome, its diagnosis and management. This represented one of the first applications of Dr. Barr's work. This disorder poses a pediatric emergency which often arises within the first few days of life. Diagnosis is based on the abnormal appearance of the genitalia which in some cases is confirmed by steroid excretion studies. With the aid of mucosal smears and identification of the presence or absence of sex chromatin, the true sex of the child can now frequently be determined. During the past 10 years eight children suffering from this disorder have been seen at this centre.

DR. G. H. VALENTINE spoke on the subject of mongolism, including the "D" and the "E" syndromes. He emphasized that this has become a rather complex subject, but with appropriate illustrations he reviewed its present status, with emphasis on recent studies. Although mongolism has been recognized for many years, the cause remains unknown. Cytogenetic studies seem to have contributed towards a clearer understanding of the etiology. Speculation regarding the role of a chromosomal anomaly was first made by Waardenburg in 1932. Today we know that in contrast to normal individuals, persons with mongolism have 47 chromosomes. It has recently been recognized that mongols have three chromosomes in the 21 position, i.e. an autosomal trisomy. There are some instances of mosaicism, but these are rare. Five patients have been reported with the "D syndrome", who have a 13-15 group trisomy, and seven have so far been reported with the "E syndrome", which is characterized by trisomy in the 17-18 group.

DR. E. PLUNKETT then discussed the Klinefelter syndrome and male infertility. This is the commonest of sex endocrine anomalies and its incidence appears to be higher among mentally defective subjects. The first three patients with this disorder were described in 1955, and to date some 35 to 40 cases have been described in the literature. In discussing the chromosomal abnormalities in this situation, Dr. Barr stated that the syndrome may be associated with an XXY, XXYY or XXXY chromosomal pattern.

DR. D. P. SWARTZ spoke on the subject of Turner's syndrome, its diagnosis and management. He emphasized that the multiplicity of attempts to devise an appropriate name for this clinical entity probably reflects a lack of understanding regarding its underlying nature. It has been referred to through the years by such terms as "congenitally aplastic ovary syndrome", "rudimentary ovary syndrome", "ovarian dwarfism", "ovarian agenesis" and others, and now may probably be appropriately referred to as the "XO syndrome". The case histories of several patients were discussed in detail, as was their appropriate management. If an infant is affected, it is a simple but delicate procedure to remedy the defect and enable the girl to lead a normal marital life. There is general agreement that this should be done before the age of three years, especially if clitoral enlargement is marked. In the discussion of Dr. Swartz' paper, Dr. Carr reviewed the details of the chromosomal anomalies that occur in Turner's syndrome. This disorder occurs much less frequently than does Klinefelter's syndrome, and the possible reasons for this observation and for the associated anomalies were discussed.

Sex anomalies in two sisters presenting varying degrees of masculinity were described by DR. E. PLUNKETT. In one sister the presence of testes was proved; these were successfully removed surgically. After careful study, the other sister was not found to have any gonads. Dr. Carr discussed the embryological significance of the findings in these two sisters.

The morning sessions terminated with an address by DR. BROCK E. BRUSH on the subject of "Islet Cell Adenomas".

In the afternoon DR. JOSEPH M. JANES of the Mayo Clinic discussed "A Surgical Approach to Vascular Anomalies of the Extremities". Since blood vessels arise from a common anlage, it is surprising that one does not encounter anomalies of the arteries and veins more

often. Leg-length discrepancies in most children are the result of poliomyelitis. Less common are those due to the presence of a congenital arteriovenous fistula. Unfortunately these are all too often multiple and frequently so extensive as to make it difficult to eradicate the condition surgically. An experimental approach in puppies was initiated in 1947 by creating a fistula between the exterior iliac artery and vein. In nine of the 10 animals in which this anomaly was induced, a longer extremity resulted. This approach was instituted in the treatment of unequal leg length in children, in 1950, and to date some 75 children have been subjected to surgical procedures to create an arteriovenous fistula in the short extremity. The fistula is allowed to remain for varying periods of time; 30 of these have now been closed. It is, of course, anticipated that all will have to be closed eventually. The maximum "catch-up" in leg length in these cases has been four centimetres. This obviously suggests that this approach is not the final answer to the problem. The main theme of Dr. Janes' presentation concerned his experience with congenital dysplastic angioplasties, of which he presented examples of several types. Surgical treatment is often not effective in the eradication of such lesions except where amputation is carried out.

DR. MURRAY BARR then spoke on "Cytogenetics and Related Topics, A Summation". Until recently, cytogenetics seemed far removed from the theory and practice of medicine. This situation has now changed and some knowledge of cell nuclei and chromosomes is necessary to provide a better insight into the cause of certain developmental abnormalities. Dr. Barr presented a most articulate and interesting general account of the role of cellular nuclei and chromosomal cytology in relation to medicine, referring extensively to the comments of previous speakers with regard to specific situations. It is clear that chromosomal abnormalities are a fact of life in present-day medicine. Their recognition is of value in diagnosis and presents a rewarding field of study and clinical investigation. It goes without saying that the research aspects of cytogenetics have just begun. Perhaps the most fruitful approach to such research will come through collaboration of the embryologist, cytologist and biochemist in an effort to learn just why the various abnormalities in the chromosome complement produce the specific type of developmental error that is associated with them. This could conceivably arise through modifications of embryonic inductors, enzyme systems and so on.

DR. BROCK E. BRUSH spoke on the subject of "Parathyroid Tumours", emphasizing the importance of their correct diagnosis and treatment. The day-long session ended with an address by SIR GEORGE PICKERING on "Acute Arterial Thrombosis and Embolism". Sir George indicated that his interest in this problem had begun with disbelief in the traditional teaching that "little strokes" were due to transient episodes of thrombosis in cerebral vessels. He had an opportunity to observe a patient who presented with episodes of visual disturbances and was able to photograph white bodies moving through the retinal arterioles. He correlated this observation in the laboratory with observations on the sequence of events following experimental injury to vessels in the mesentery of rabbits. A coloured motion picture film demonstrated the development, at the site of vascular injury, of masses composed of platelet thrombi and the amazingly continuous production of small platelet emboli streaming off from such traumatic sites.

The interest and appreciation of the audience was demonstrated throughout by the capacity attendance, by the volume of questions directed to the speakers, by the activity of the discussions, and by numerous outbursts of spontaneous applause. A. H. NEUFELD

BOOK REVIEWS

LISTERIOSIS. H. P. R. Seeliger, with an introduction to the 2nd German edition by Prof. Dr. H. Eyer. 308 pp. Illust. Hafner Publishing Company, Inc., New York, 1961. $14.25.

This important and timely monograph, two German editions of which appeared in rapid succession in 1955 and 1958, has been brought up to date and now is published for the English-speaking microbiologist, physician and veterinary surgeon. It is important because, since E. G. D. Murray's classical description in 1926, *Listeria monocytogenes* has been recognized in epizootic reservoirs of global distribution. It is timely because medical interest has lately become stimulated in this elusive bacterial pathogen as the offender in serious human disease, such as septicemia, meningoencephalitis, listeriosis of the newborn and during pregnancy, with incrimination of *L. monocytogenes* as the cause of many cases of habitual abortion.

Based on extensive personal studies and experience of the author, on 537 quoted papers and direct communications, and listing further 66 recent publications, this thorough monograph summarizes the modern knowledge and concept of listeriosis in a fluent style, aided by well-chosen figures and extensive tables. Twenty pages of subject-index are helpful for rapid reference. The book is arranged in four parts. The first describes the agent, its biological criteria, toxicity and pathogenicity. Due credit is given to the contributions of many workers. The second part deals with listeriosis in animals and covers the distribution of the epizootic in tabulated detail. Its importance in wild life and domestic animals is shown. Clinical descriptions and outlines for treatment, prevention and control are given. This part is also very useful for the epidemiologist who wishes to study the occurrence of *L. monocytogenes* in humans, where it now is recognized as an elusive, often mistaken, but seemingly common pathogen. The diverse clinical manifestations in man are listed and described in part three, tabulating again the reported findings on a global scale and quoting details of many cases. This portion of the book makes for impressive reading, notably the chapters on listeriosis of the new-

born and during pregnancy. The difficulties and pitfalls of its recognition are mentioned. Comprehensive chapters deal with the pathology, epidemiology, therapy and suggested control measures of human listeriosis. These should build up the interest of every bacteriologist towards part four, where the author's great experience is reflected in the chapters on isolation, recognition, typing and serological evidence of Listeria. Various approaches are presented in remarkable detail, so that this part of the book should prove valuable as a manual in the bacteriological laboratory. Together with part one, it also covers the scope of international teamwork in Listeria research, enabling workers in the field to turn to reference centres for advice, guidance or material help. The author himself, as befits a student of many months in Professor E. G. D. Murray's laboratory at McGill University, has become an authority on the subject of listeriosis. This monograph should foster intensified research and clinical awareness of listeriosis, serving as the valuable reference manual it was intended to be and, in fact, is.

ORAL MEDICINE. Diagnosis and Treatment. 4th ed. Lester W. Burket. 608 pp. Illust. J. B. Lippincott Company, Philadelphia and Montreal, 1961. $15.00.

This new edition of "Oral Medicine" continues the author's philosophy of diagnosis and treatment of lesions in and about the oral cavity. Here the interests of the dentist and physician meet on common ground. Primary oral lesions as well as secondary manifestations of systemic diseases are discussed in a manner intended to acquaint the dentist with his share of the problem so that he and the physician may co-operate effectively for the betterment of the patient.

Frequently the dentist is the first person to see the oral signs of systemic disease and thus has the responsibility for making an early diagnosis even though he may not undertake the actual treatment. He is, however, in a position to advise regarding the effects on the dentition as a whole.

Only one of the 13 sections deals with exclusively dental disturbances. The balance is devoted to diseases of the organ systems, nutritional and metabolic disturbances, pedodontics, gerodontics, and occupational hazards. One entire section deals with the problem of oral cancer with special emphasis on the diagnostic phase. Here too, the dangers of post-radiation osteonecrosis are considered in the light of the special problems posed by the presence of teeth.

Anyone interested in the field of oral medicine can profit by consulting this lucid and concise text.

POSTURAL FITNESS. Significance and Variances. C. LeRoy Lowman, Chief of Staff, Orthopedic Hospital, and C. H. Young, Professor of Physical Education, University of California, Los Angeles. 341 pp. Illust. Lea & Febiger, Philadelphia; The Macmillan Company of Canada Limited, Toronto, 1960. $7.50.

This is an extremely well written and informative presentation of current medical and lay problems related to normal postural mechanics and deviations therefrom. Certainly it will satisfy a wide range of readers, whether they be parents, teachers, therapists, instructors, nurses or physicians.

Occasional controversial topics are dealt with, such as the deleterious effects on the mechanics of the foot caused by barefoot-walking by young persons. However, the author's facts are so convincingly presented that they make for stimulating and provocative reading. On the whole, the topic has been learnedly presented and pictorialized. From the medical viewpoint, one might suggest the addition of anatomical diagrams of muscles, bones and joints in the normal subject with contrasting deviations from the normal. The provision of more detail on muscle, connective tissue, joint and bone histology would give a deeper insight in the normal and abnormal biomechanics of the functional motor system of the human body, including normal gait.

The "success" of the message in this book will depend on the interest of the parent, the education of the school nurse and the ethical discretion of the physical educationalist, subject to the recognition of dangers of making a lay diagnosis and institution of remedial exercises without medical confirmation.

The reviewer has no hesitation or reservation in recommending this book as an important reference for the medical undergraduate student. It should be included in every school library.

The references and extended reading material recommended at the end of each chapter should leave no doubt in the minds of the readers concerning the author's sound authenticity and insight in the problem of physical fitness.

MEDICAL-SURGICAL NURSING. 2nd ed. Kathleen Newton Shafer, Janet R. Sawyer, Audrey M. McCluskey and Edna Lifgren Beck. 876 pp. Illust. The C. V. Mosby Company, St. Louis, Mo., 1961. $8.75.

The authors have succeeded admirably in producing in this edition of "Medical-Surgical Nursing" a most useful text for students. The first section, consisting of four chapters, provides a focus around which the nursing care of all patients may be centred. It deals in simple terms with the complex role concepts of the patient and the nurse, emotional responses to illness and the nurse's part in relieving anxiety. The nursing needs of the ageing, the chronically ill, and the patient requiring rehabilitation are considered simply yet succinctly. All the concepts presented in the first section are meaningful strands which will help the teacher and the student to keep in mind the patient as an individual with varying needs.

The second and larger section is devoted to the nursing care of patients with specific medical and surgical conditions. The authors have integrated the medical and surgical aspects so well that the usual repetition of content has been eliminated. Sufficient factual material about various conditions is given to form a basis for the general nursing care which is dealt with in sufficient detail to be most helpful. Students using this text will have no difficulty achieving a clear concept of comprehensive nursing care. Excellent references provide the reader with sources of more detailed knowledge of medical content.

The book is large and rather heavy to handle, but the double-column arrangement of the pages makes for ease of reading. The topic headings stand out and the illustrations are well chosen. Study questions for review are included at the beginning of each chapter in section II.

The book is eminently suitable for the use of both teachers and students. Teachers will find it helpful in developing integrated courses in medical and surgical nursing. Students will find it useful because so much pertinent information has been assembled in one book.

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Vitamin B_1	1 mg.
Vitamin B_2 — Riboflavin	1.5 mg.
Vitamin B_6 — Pyridoxine	1 mg.
Niacinamide	6 mg.
d-alpha-tocopheryl acid succinate (anti-oxidant)	2 mg.

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(Lowenstein, L., Pick, C. and Philpott, N. W.: Am. J. Obst. and Gynec. 70:1309, 1955)

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MEDICAL NEWS *in Brief*

(Continued from page 1463)

DRUGS IN PREGNANCY. THEIR EFFECTS ON THE FETUS AND NEWBORN

In considering drug therapy for pregnant women, it must be borne in mind that almost all chemical compounds in use as therapeutic agents pass from the maternal to the fetal circulation through the placenta. These drugs can produce a wide range of harmful effects on the fetus and neonatal infant. The effects of some substances for which we have data reflecting a deleterious effect are listed by Sandberg (*California Med.*, 94: 287, 1961).

It is suggested that in the future more caution be exercised in using drugs during pregnancy and that in histories, both obstetrical and pediatric, any therapy given to the mother during gestation be recorded in detail.

—

ELECTRONIC COMPUTER TO AID IN REDUCING NEONATAL DEATHS

Evaluation of medical data collected by electronic computer under a program directed by Dr. Sydney H. Kane and sponsored by the American Medical Research Foundation in co-operation with the UNIVAC Division of Remington Rand aims at reducing neonatal morbidity and mortality.

The use of a UNIVAC Solid-State computer makes possible correlation of data on 150,000 deliveries in hospitals scattered throughout the nation, while maintaining anonymity for all doctors, patients and member institutions. To date, data from 50,000 births at 90 participating hospitals have been reduced to the media of punched cards.

These cards contain information on age of mother, maternal complications, type of delivery and anesthetics used.

"We hope," states Dr. Kane, "to reduce newborn deaths by at least 12 to 14,000 annually through the means of electrical data processing in addition to obtaining vast amounts of data for additional research purposes."

Dr. Kane comments that the study is the first, anywhere in the world, to avail physicians of information on the cause of every infant death reported in the participating units. The study provides the physician with the opportunity for individual evaluation in a climate of local hospital conditions. Eventually, information will be available on cases with an incidence as low as 10 in 4,000,000.

UNIVAC conclusions deduced from data supplied by this study are sent to participating institutions.

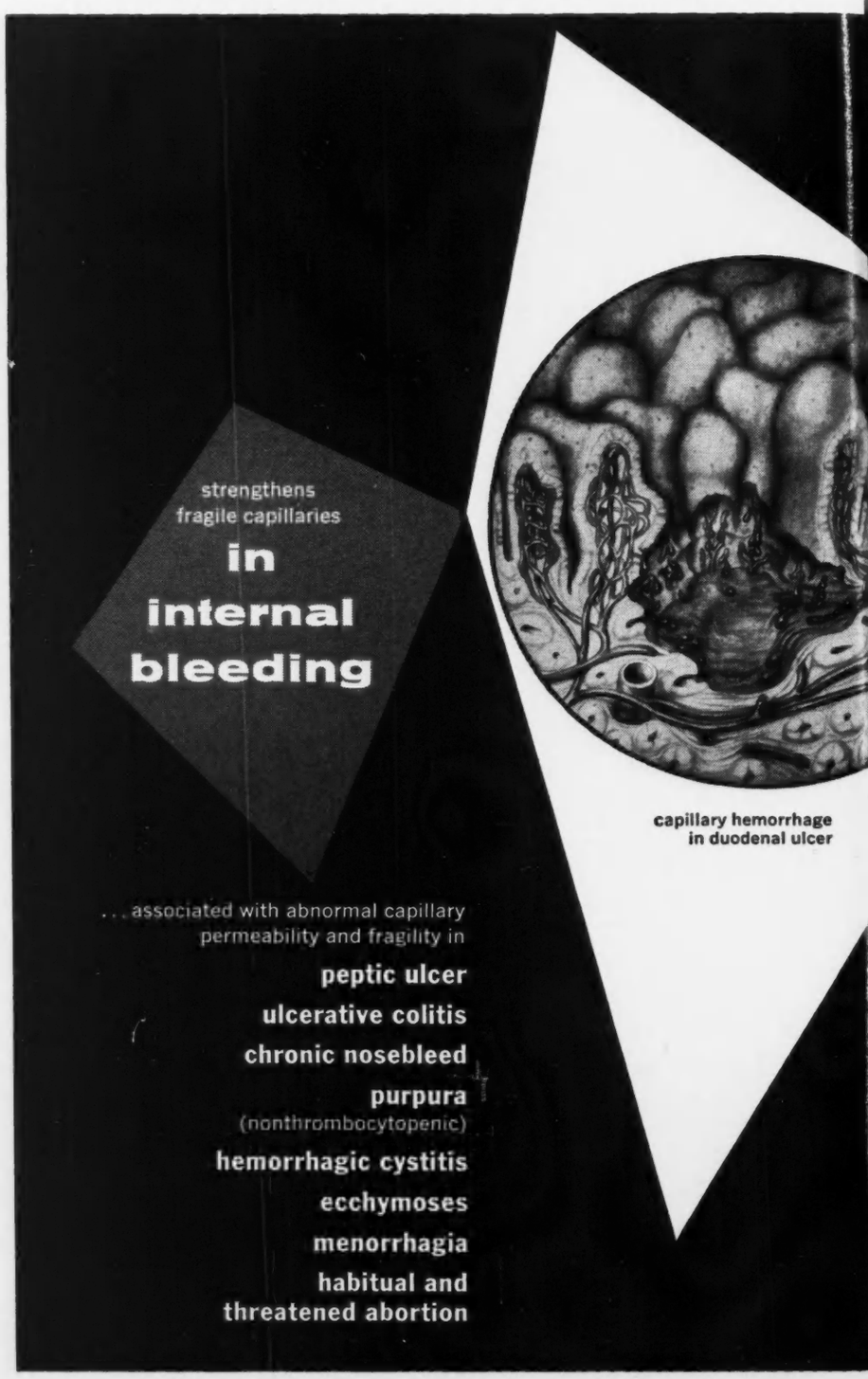
Other benefits include research into drug therapy and diverse medical techniques, evaluation of maternity and newborn procedures and exposure of physicians to electronic data processing methods.

HEALTH RECORD OF SCHOOL-AGE CHILDREN

The health record of school-age children in the U.S.A. is better now than ever before, according to statisticians of the Metropolitan Life Insurance Company.

In the decade since 1948-49, mortality to ages 5-14 years has declined by about one-third. The average annual death rate at these ages during 1958-59 was less than 6 per 10,000 boys and less than 4 per 10,000 girls.

The downward trend of mortality from disease—especially in-



fectious diseases—has been more marked than from accidents and other external causes. In the last decade, the death rates from tuberculosis and from acute poliomyelitis dropped 90% among school-age children. Mortality from pneumonia declined by one-third, while the rates from appendicitis and heart disease showed reductions of about 75%. There have been unfavourable trends, however, in the recorded increases in the mortality from cancer and from congenital malformations.

Cancer, including leukemia, now leads all diseases as a cause of death in school-age groups, and accounts for approximately one-fourth of all deaths from disease. Congenital malformations are next in rank, and pneumonia third.

Despite lower mortality rates, school children are subject to a higher frequency of acute illness than older persons. The National Health Survey in the year July 1958-June 1959 showed that the incidence of acute illness at ages 5-14 averaged three per child. More than half of these were accounted for by respiratory diseases and a little more than one-tenth by injuries. The Survey also revealed that the corresponding school time lost because of the illnesses averaged 5.3 days per child.

PAHO TO SPEND $13,178,869 DURING 1962

The Pan American Health Organization will spend $13,178,869 in assisting the American Republics in carrying out 303 health projects during 1962.

Announcement of the Organization's 1962 budget was made by Dr. Abraham Horwitz, Director of the Pan American Sanitary Bureau, PAHO's operating arm and Regional Office for the Americas of the World Health Organization.

The Director told delegates to the 13th Annual Meeting of PAHO's Directing Council that the 1962 figure represents an increase of 7.9% over the 1961 budget of $12,246,747. It also increases the number of projects by 49 over the 254 administered by PAHO/WHO during 1961.

PAHO's Directing Council is made up of the health representatives of the 21 American Republics, plus those of France, the Netherlands and the United Kingdom, on behalf of their territories in this hemisphere. The Council met in Washington from October 3-17.

PAHO receives its funds from four sources:

1. The PAHO regular budget which comes from the quota assessments of the Organization's member states. For 1962 this portion of the budget represents $5,240,000. This amount was approved by the Directing Council.

2. The PAHO other funds budget which is made up of the Special Malaria Fund for the Americas—$2,616,377 for 1962; the Community Water Supply Fund—$362,326; Technical Co-operation Funds received from the Organization of American States—$650,661; the budget and related grants of the Institute of Nutrition of Central America and Panama—$527,300; and grants and other contributions to the Organization—$371,314. This total for 1962 is $4,527,978.

3. The funds the Pan American Sanitary Bureau receives from WHO as its Regional Office, which will amount to $2,249,000 for 1962.

4. The United Nations Technical Assistance Funds received by PAHO through WHO. This figure for 1962 is $1,161,891.

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